A STUDY ON CLINICAL PROFILE OF TUBERCULOSIS IN HIV CHILDREN

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in fulfillment of the regulations
for the award of

M.D DEGREE IN PAEDIATRIC MEDICINE

BRANCH VII

GOVERNMENT MOHAN KUMARAMANGALAM

MEDICAL COLLEGE, SALEM.

MARCH 2010

CERTIFICATE

Certified that this dissertation entitled "**A STUDY ON CLINICAL PROFILE OF TUBERCULOSIS IN HIV CHILDREN"** is a bonafide work done by **Dr.M.NIRMALA** post graduate student of Paediatric Medicine, Government Mohan Kumaramangalam Medical College, Salem-636030, during the Academic year 2008-2010.

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DECLARATION

I declare that this dissertation entitled "**A STUDY ON CLINICAL PROFILE OF TUBERCULOSIS IN HIV CHILDREN"** done by me at Government Mohan Kumaramangalam Medical College Hospital, Salem under the guidance and supervision of my department chiefs **Prof.R.SIVAGAMASUNDARI, Prof.M.RATHINASAMY.** It is submitted in part of fulfillment of the award of the degree of MD (Paediatrics) for the March 2010 examination to be held under The TamilNadu Dr. MGR Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other university.

(Dr.M. NIRMALA)

ACKOWLEDGEMENT

I gratefully acknowledge and sincerely thank our beloved Former Dean, **Dr.P.SHANMUGAM, M.S., M.Ch.,** Govt. Mohan Kumaramangalam Medical College and Hospital, for kindly giving me the permission for conducting this study.

I am also thankful to **Dr. K.V.KANAGASABAI, M.D.,** Present Dean, Govt.Mohan Kumaramangalam Medical College and Hospital, for his whole hearted co-operation and support for the completion of this dissertation.

I am grateful to **Prof.Dr.R.SIVAGAMASUNDARI, M.D., DCH.,** Prof. and Head of the Department of Pediatric Medicine, Govt. Mohan Kumaramangalam Medical College and Hospital, for permitting me to do the study and for her encouragement.

I am sincerely grateful to Associate Professor **Dr.M.RATHINASAMY, M.D., DCH.,** for his guidance and help in conducting this study.

I extend my sincere thanks to Registrar **Dr. T.S.SUNDARARAJAN, M.D., D.C.H.,** for his valuable suggestions and guidance.

I am extremely thankful to all the Assistant Professors of Pediatrics for their valuable guidance and encouragement.

I express my sincere thanks to **Dr.L.ARUNACHALAM,M.D.,(S.T.D.)** and all medical officers, ART centre, for their help in conducting the study.

I express my sincere thanks to **Dr.K.ARUNAGIRI, J.D.,** District T.B. Centre for his valuable help in conducting the study.

I am also thankful to my colleagues for their full cooperation in this study and my sincere thanks to all the patients who cooperated for this study.

CONTENTS

ABBREVATIONS

HIV	: Human Immunodeficiency Virus
TB	: Tuberculosis
PTB	: Pulmonary Tuberculosis
TST	: Tuberculin Skin Test
PCR	: Polymerase Chain Reaction
AIDS	: Acquired Immuno Deficiency Syndrome
WHO	: World Health Organization
CMI	: Cell Mediated Immunity
CXR	: Chest X-Ray
RNA	: Ribo Nucleic Acid
LTBI	: Latent Tuberculosis Infection
DTH	: Delayed Type Hypersensitivity
DOTS	: Directly Observed Short term Therapy
PI	: Protease Inhibitor
NNRTI	: Non Nucleoside Reverse Transcriptase Inhibitor
IPT	: Isoniazid Preventive Therapy
ART	: Anti Retroviral Therapy
HAART	: Highly Active Antireteroviral Therapy

INTRODUCTION

HIV is driving TB epidemic in many countries, especially in sub-saharan Africa and increasingly, in Asia and South America. TB in populations with high HIV prevalence is a leading cause of morbidity and mortality.

Children who are HIV infected have a higher risk of progression after primary infection. Children born to HIV positive parents who are not infected with TB themselves, are also at higher risk of acquiring TB because of exposure. The source of transmission of TB to a child is usually an adult with sputum-smear positive PTB. Cases of TB in children represent between 10% to 20% of all TB cases.

Extrapulmonary TB manifestations are Lymphadenopathy, Pleural effusion, Miliary TB, TB meningitis, TB Abdomen, Disseminated TB, Potts Spine.

AIM OF THE STUDY

1. To evaluate the clinical, bacteriological and radiological pattern of TB in HIV seropositive children in correlation with CD4 count.

2. To find out the trends of TB infection in HIV seropositive children in GMKMCH, Salem.

3. To find out the prevalence of TB among HIV seropositive children in our hospital.

REVIEW OF LITERATURE

TUBERCULOSIS: An overview

Tuberculosis has been present in humans since antiquity, as the origin of the disease are in the first demonstration of cattle (which also gave human viral pores). Skeletal remains show prehistoric humans (4000BC) had TB[1] and tubercular decay has been found in the spines of Egyptian mummies from 3000-2400BC[2]. There were references to TB in India around 2000 BC and indications of lung scarring identical to that of modern day TB sufferers in preserved bodies (such as mummies) suggests that TB was present in the Americans from about 2000 BC. Phthisis is a Greek term for consumption. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times which was almost always fatal[3].

Due to the variety of the symptoms, TB was not identified as a single disease until the 1820's and was not named tuberculosis until 1839 by JL Schonlein[4]. The bacillus causing tuberculosis, Mycobacterium tuberculosis, was identified and described on March 24, 1882 by Robert Koch. He received the Nobel Prize in physiology (or) medicine in 1905 for his discovery[5].

The other names for tuberculosis are:

TB (short for tuberculosis and also for Tubercle Bacillus).

Consumption (TB seemed to consume people from within with its symptoms of bloody cough, fever, pallor and long relentless wasting).

Wasting disease.

King's evil.

White Plague (TB sufferers appear markedly pale)

Phthisis (Greek for consumption) and phthisis pulmonalis.

Miliary TB (X-ray lesions look like millet seeds) [6].

Koch's disease named after Robert Koch who discovered the tuberculosis bacilli[7].

PATHOGENESIS:

While only 10% of TB infection progresses to TB disease[8], if untreated the death rate is 51%[9].The primary complex of tuberculosis includes local infection at the portal of entry and the regional lymph nodes. TB infection begins when the MTB bacilli reach the pulmonary alveoli, infecting alveolar macrophages [8, 10], where the mycobacteria replicate. The primary site of infection in the lungs is called the Ghon

focus, which is the combination of a parenchymal pulmonary lesion and a corresponding lymph node site.

The tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels to the more distant tissues and organs where TB disease could potentially develop: lung apices, peripheral lymph nodes, kidneys, brain and bone [8,11] .

Tuberculosis is classified as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding infected macrophages. The granuloma functions not only to prevent dissemination of mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes (CD4 +) secrete a cytokine such as interferon gamma, which activates macrophages to destroy the bacteria with which they are infected[12], making them better able to fight infection. T lymphocytes (CD8 +) can also directly kill infected cells by secreting perforin and granulysin[13].

Importantly, bacteria are not eliminated within the granuloma, but can become dormant resulting in a latent infection[8]. Latent infection can be diagnosed by tuberculin skin test, which yields a delayed hypersensitivity type response to purified protein derivatives of M.

tuberculosis in an infected person.Another feature of the granulomas of human tuberculosis is the development of cell death, also called necrosis, in the centre of tubercles. To the naked eye this has the texture of soft white cheese and was termed caseous necrosis[14].

If TB bacteria gain entry to the blood stream from an area of tissue damage they spread through the body and set up myriad foci of infection, all appearing as tiny white tubercles in the tissues. This is called as miliary tuberculosis and has a high case fatality.

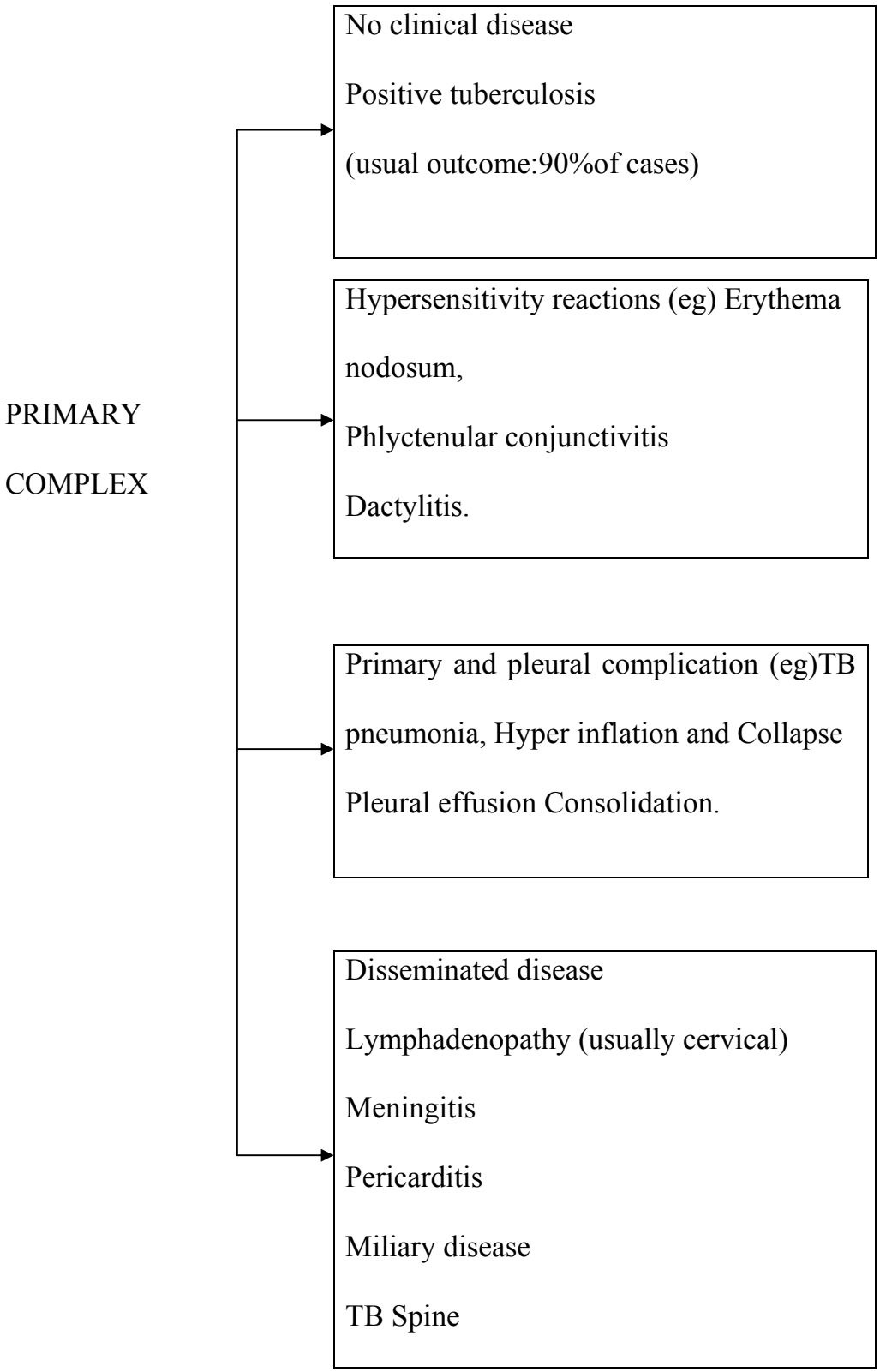
PROGRESSION:

In children in whom TB bacilli overcome the immune system defenses and begin to multiply, there is progression from TB infection to TB disease. This may occur soon after infection (primary TB disease-1 to 5%) or many years after infection (post primary TB, secondary TB, reactivation TB disease of dormant bacilli-5 to 9%). About five percent of infected persons will develop TB in first two years and another five percent will develop disease later in life. In another words about 10% of infected persons with normal immune systems will develop TB disease in their lifetime[8].

Some medical conditions increase the risk of progression to TB disease. In HIV infected children the rate of tuberculosis disease is 30 times higher than in non HIV infected children. Other conditions such as prolonged corticosteroid therapy, immunosuppressive therapy, leukemia, Hodgkins disease, end stage renal disease, recent TB infection, (within two years, or history of inadequately treated TB),chest Xray suggestive of previous TB (fibrotic lesion and nodules),chronic malabsorption syndrome or low body weight (10%or more below the ideal).

Primary complex includes the parenchymal pulmonary focus and the regional lymph nodes[15]. About 70% of pulmonary foci are subpleural and localized pleurisy is common. The hallmark of primary tuberculosis is the relatively large size of regional lymphadenitis compared with the relatively small size of initial lung focus

Children may have lobar pneumonia without impressive hilar lymphadenopathy. If primary infection is destructive , liquefaction of the lung parenchyma can lead to the formation of a thin walled primary tuberculosis cavity. Rarely, bullous tuberculous lesions can occur in lungs and lead to pneumothorax if they rupture[15] Erosion of a parenchymal focus of tuberculosis into a blood or lymphatic vessel may result in dissemination of the bacilli and a miliary pattern.


PRIMARY
COMPLEX
No clinical disease
Positive tuberculosis
(usual outcome:90%of cases)
Hypersensitivity reactions (eg) Erythema nodosum,
Phlyctenular conjunctivitis
Dactylitis.
Primary and pleural complication (eg)TB pneumonia, Hyper inflation and Collapse
Pleural effusion Consolidation.
Disseminated disease
Lymphadenopathy (usually cervical)
Meningitis
Pericarditis
Miliary disease
TB Spine

More than 50% of infants and children with radiologically moderate to severe pulmonary TB have no physical findings and are discovered only by contact tracing .Non productive cough and dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia and decreased activity occur less often .

Older children and adolescents with reactivation tuberculosis are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis and chest pain than children with primary pulmonary TB.

POST-PRIMARY TB

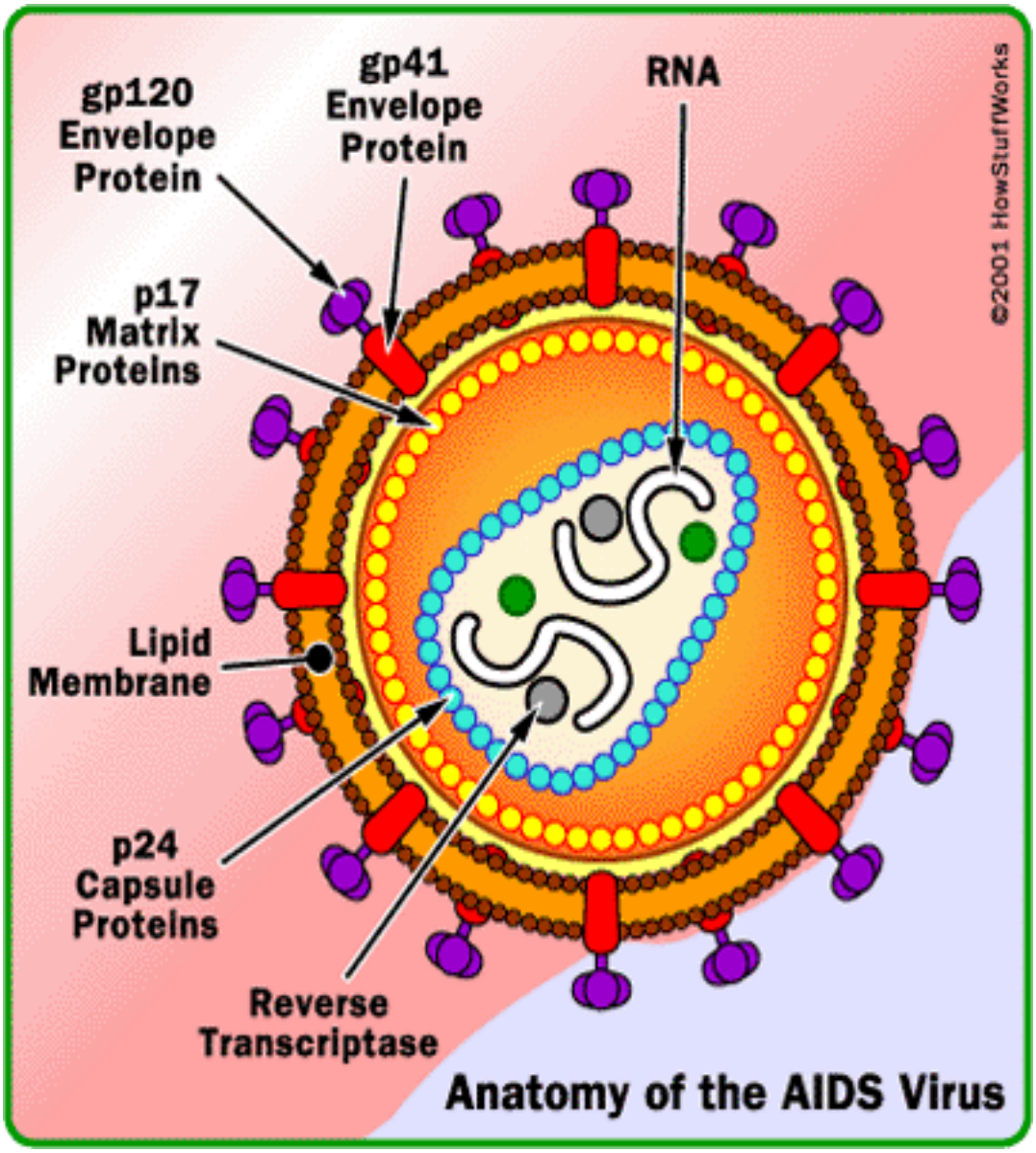
PULMONARY TUBERCULOSIS
(eg) Cavities Upper lobe infiltrates Fibrosis Progressive pneumonia Endobronchial

EXTRAPULMONARY TB	
COMMON	**LESS COMMON**
Pleural effusion	Empyema
Lymphadenopathy (usually cervical)	Kidney
Central nervous system (Meningitis,tuberculoma)	Adrenal gland
Pericarditis (Effusion/pericarditis)	Skin (lupus vulgaris, tuberculids, miliary)
Gastrointestinal (ileocaecal, peritoneal)	

DIAGNOSIS:

A complete evaluation of TB includes a history of contact with adult TB, a physical examination, clinical features, a tuberculin skin test, a chest x-ray, serological test and microbiological smears and cultures. The interpretation of the tuberculin skin test depends upon the persons risk factors for infection and progression to TB disease, such as exposure to other cases of TB or immunosupression[16] .Tuberculin tests have the disadvantage in that they may produce false negatives, especially when the patient is co-morbid with malnutrition, sarcoidosis, Hodgkins lymphoma or most notably active tuberculosis disease[8]. New TB tests are being developed that offer the hope of cheap ,fast and more accurate TB testing. These include PCR detection of bacterial DNA ,and assays to detect the release of interferon gamma in response to mycobacterial proteins such as ESAT-6[17].These are not affected by immunization or environment mycobacteria, so generate fewer false positive results[18]. The development of a rapid and inexpensive diagnostic test would be particularly valuable in the developing world[19].

HIV-AN INTRODUCTION



Ever since the first description of AIDS in 1981,researchers have identified two types of HIV. HIV-1 Subtype C is the predominant type worldwide. HIV-2 occurs mostly in West Africa and occasional infections have occurred in Africa, Europe, Asia, and Latin America. Both types cause AIDS and the routes of transmission are the same.

EPIDEMIOLOGY

The WHO estimated that more than 39 million persons worldwide were living with HIV infection at the end of 2008, including 2.2 million children < 15 years of age[15]. Sub-saharan Africa accounts for the fastest growing epidemic, with almost 90% of worlds total population of HIV infected children. India and Thailand dominate the epidemic in Southeast Asia.

Virtually all HIV infections in children < 12 years of age are the result of vertical transmission from an HIV infected mother. A vanishing minority of children are infected by contaminated blood products and or clotting factors. The risk of transmission without Breast Feeding is 20-25%, with Breast Feeding for 6 months is 25-30% and the risk increases to 30-35% with prolonged Breast feeding for 18-24 months.[15]

The risk of transmission can be reduced to 1% by:

a) ARV prophylaxis to women during pregnancy/labour and to the infant in first week.

b) Elective caesarean section – prior to onset of labour and rupture of membranes

c) Complete avoidance of Breast feeding.

The clinical consequences of HIV infection are due to the ability of this virus to disarm the host immune system, a process that occurs by virtue of the fact that the primary target for the virus is the helper induced subset of lymphocytes. This lymphocyte subset, defined by its surface expression of the CD4 molecule, acts as the pivotal orchestrator of a myriad of immune functions. HIV infection can therefore be considered a disease of the immune system, characterized by the progressive loss of CD4 + lymphocytes, with ultimately total consequences for the infected host[8].

Despite the immunosuppression induced by HIV, a number of specific immunologic defences against the virus are generated in infected individuals and may contribute to the long asymptomatic phase following infection by keeping the virus atleast partially contained. The hallmark of HIV infection is progressive depletion of the CD4 helper inducer subset of lymphocytes. Because of the central

role of these cells in immunologic functioning, the clinical disease manifestation of immunosuppression and susceptibility to opportunistic infections and neoplasms are not surprising. The immunologic deficit associated with HIV infection are wide spread and involve numerous interdependent effector arms of the immune system, including both cellular and humoral elements.

Of all the opportunistic infections in persons infected with HIV virus, tuberculosis remains the commonest[20]. HIV probably increases the susceptibility to primary infection with M-tuberculosis, as well as to reactivation of TB infection due to depressed CMI[21,22]. HIV increases the risk of progression of M-tuberculosis infection to TB disease. This risk increases with increasing immunosuppression. HIV increases not only the risk but also the rate of progression of recent or latent M-tuberculosis infection to disease.

WHO staging system for HIV infection and related disease in children younger than 13 years[23,24].

Two Classifications

i) WHO Classification – Symptomatic HIV divided into four stages based on the severity of the symptoms.

ii) CDC Classification – Clinical classification and immunological classification based on CD4.

Revised WHO Clinical Staging of HIV/AIDS for Infants and Children with Confirmed HIV infection (> 18 months of age – HIV Antibody Test Positive, < 18 months of age – Virologic Test Positive)[23]

CLINICAL STAGE 1 (AYSMPTOMATIC)

- Asymptomatic
- Persistent generalized lymphadenopathy

CLINICAL STAGE 2 (MILD)

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Linear gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

CLINICAL STAGE 3 (ADVANCED)

- Unexplained moderated malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6-8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node TB
- Pulmonary TB
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV – associated lung disease including bronchiectasis
- Unexplained anemia (<8g/dl), neutropenia (<0.5x$10^9/L^3$) or chronic thrombocytopenia (<50 x $10^9/L^3$)

CLINICAL STAGE 4 (SEVERE)

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia

- Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extra pulmonary TB
- Kaposi's sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or CMV infection affecting another organ, with onset at age over 1 month.
- Extra pulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV – associated nephropathy or HIV – associated cardiomyopathy

IMMUNOLOGICAL CLASSIFICATION BASED ON CD4[23]

Immunologic Definitions	< 12 months		1-5 years		6-12 years	
	µL	%	µL	%	µL	%
No evidence of suppression	≥1500	≥25	≥1000	≥25	≥500	≥25
Evidence of moderate suppression	750-1499	15-24	500-999	15-24	200-499	15-24
Severe suppression	<750	<15	<500	<15	<200	<15

WHO case definitions for AIDS in children where HIV testing facilities are not available.

MAJOR SIGNS:

- Weight loss > 10% of body weight or failure to thrive
- Chronic diarrhea (> one month)
- Prolonged fever (> one month)
- Severe or repeated pneumonia

MINOR SIGNS:

- Generalised lymphadenopathy
- Oro – Pharyngeal candidiasis

- Repeated common infections (otitis, pharyngitis etc.,)
- Generalised dermatitis
- Confirmed maternal HIV infection.

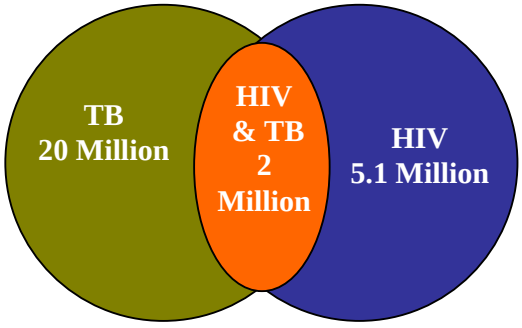
Pediatric AIDS is suspected in an infant or child presenting with atleast two major signs associated with atleast two minor signs in the absence of known cases of immunosuppression.

These definitions detect the presence of symptomatic AIDS and not HIV infection itself and are confounded by malnutrition, diarrheal diseases and tuberculosis.

PRACTICAL POINT:

The term AIDS is used for epidemiological surveillance, not for clinical case. For patients with TB, persistent cough for more than one month should not be considered as a minor sign.

Picture showing estimated HIV & TB coinfection in India[25]



Features	Stage of HIV Infection	
	Early	**Late**
Clinical Presentation	Often resembles post primary TB	Often resembles primary TB; Extra pulmonary TB common
Sputum smear result	Often positive	Often negative
CXR	Often shows cavities	Atypical often infiltrates, Lower lobe lesions or intrathoracic lymphnodes

EPIDEMIOLOGY:

About a third of the HIV positive population worldwide is co-infected with M-tuberculosis. This accounts to about 14 million people worldwide. Globally, 9% of all tuberculosis cases in adults are attributable to HIV[26]. Studies from sub-saharan Africa have recorded HIV seroprevalance rates of 50 - 70% in patients with tuberculosis. In Asia, where the HIV epidemic is still at early stage, the rate of HIV infection in TB patient has been lower.

A HIV positive person infected with M-tuberculosis has a 50-60% lifetime risk of developing TB disease as compared to an HIV negative person who has only a 10% risk.

Using estimates of prevalence of TB and HIV in various regions, It has been observed that by mid-1994 there were 5.6 million persons co-infected with HIV and TB worldwide, more than 1.15 million of these live in South-east Asia (including India)[27]. The proportion of HIV-attributable tuberculosis death will increase from 4.6% to 14.2%.

In India the rates of HIV-tuberculosis co-infection is steadily increasing. In Pune the prevalence of HIV infection among tuberculosis patients increased from 3.2% in 1991 to 20.1%[28]. Most available data on HIV and TB is from adults. Disease in children follows progressions of primary infection. It is estimated that worldwide there will be over 56,000 cases of HIV attributable tuberculosis annually in children by 2006[29]. A study from Mumbai showed a prevalence of HIV of 18% among children with CNS tuberculosis or miliary tuberculosis; the prevalence HIV seropositivity among children with chronic diarrhea in same study was 24%[30].

TUBERCULOSIS IN HIV INFECTION:

HIV has had as substantial effect on the incidence clinical manifestations, treatment and outcome of TB. Globally, HIV and TB

are the 2 leading infectious causes of death.People who are infected with HIV are at increased risk of contracting TB.

Co-infection with these pathogens can be particularly devastating, especially in the developing world, where the burden of disease is high and access to effective therapy in low. Among infection associated with HIV, TB is unique in that it may be transmitted to immunocompetent persons via the respiratory route, and is easily treatable once identified, may occur in early stage HIV- disease and is preventable with drug therapy. However, multidrug resistance tuberculosis is a potentially serious problem, even though its incidence has declined because of the use of directly observed therapy and other improved practices[31.]

TB is a major opportunistic infection in HIV-infected patients often representing their AIDS defining illness and the first indication of immunodeficiency. Epidemiology, clinical manifestations and management of TB are altered in HIV-infected patients.

IMPACT OF HIV ON TB

HIV is the most significant risk factor for progression from sub-clinical infection with mycobacterium tuberculosis to active TB.[22]

However, when a person is dually infected with HIV and M-tuberculosis, the risk of developing TB significantly increases from 10% in a lifetime to 5-15% per year[31].

HIV infected children are at markedly increased risk for primary or reactivation tuberculosis and for second episodes of tuberculosis from exogenous reinfection[32].

The lifetime risk for progression to active TB among HIV-negative persons likely infected with M-tuberculosis is estimated at 10%. In contrast, among HIV infected children the risk for progression to active disease is approximately 10% per year, and the immediate risk for progressive primary disease after recent infection with M-tuberculosis approaches 40%[33].

This interaction between TB and HIV accounts for much of the recent global resurgance in TB of late, however HIV infection does not

increase the infectiousness of persons with active TB. The introduction of potent combination Anti-retroviral therapy in developing world, which has dramatically decreased the risk for opportunities infections and death among HIV infected children, has also decreased the risk for developing active TB and the risk for death among HIV infected persons who develop active TB.

Children born to HIV infected mother but who are not infected, are also at higher risk of acquiring tuberculosis because of the increased risk of exposure to tuberculosis from their parents. It is estimated that tuberculosis rate in the first four years of life among children born to HIV infected mothers is 10 times higher than in non HIV infected and 30 times higher in HIV infected children as compared to other children.

PATHOGENESIS:

Tuberculosis can develop through progression of recently acquired infection (primary disease), reactivation of latent infection, or exogenous reinfection.

Infection with M-tuberculosis can occur when a child is exposed to an infectious case of TB particles (<5 cm in size) containing the tubercle bacilli. If the bacilli reach the pulmonary alveoli, they may be ingested by alveoli macrophages the first line of defence against M-tuberculosis. Surviving tubercle bacilli multiply within the macrophage and eventually undergo hematogenous spread to other areas of the body.

After ingestion, alveoli macrophages present the mycobacterial antigens to CD4 + T cells. This results in the release of interferon gamma (IFN γ) which in turn activities macrophages to control the mycobacterial infection. However the activated macrophages also release interleukin – 1 which enhances HIV replication. Mycobacteria also enhance HIV replication by inducing nuclear factor kappa-B, the cellular factors that bends the promote region of HIV[34,35].

Susceptibility to TB is related to the pattern of cytokines produced by T lymphocytes. CD4 + lymphocytes which produce interferon-γ are central to antimycobacterial immune defenses and fatal mycobacterial disease develops in children who lack the interferon γ receptor. In contrast to CD4+lymphocytes, CD8 + lymphocytes, which produce interleukin -4 and interleukin -10 do not contribute to anti mycobacterial immunity. When peripheral blood lymphocytes from HIV infected patients with tuberculosis are exposed to M-tuberculosis in vitro, they produce less interferon–γ but similar amounts of interleukin-4 and interleukin-10, as compared with lymphocytes from HIV- negative patients with tuberculosis. These findings suggest that the reduced CD4 response in HIV-infected patients contributes to their susceptibility to TB.

The hallmark of HIV infection is progressive deterioration and depletion of CD4cells, coupled with defects in macrophage and monocyte function. There is evidence that the immune response in patients with TB might enhance HIV viral replication and accelerate the natural progression of HIV infection [36].

TUBERCULOSIS AND THE COURSE OF HIV INFECTION:

Exposure of alveolar macrophages and lymphocytes from HIV infected patients to M.Tuberculosis in vitro upregulates retroviral replication[34,35]. TB has been associated with a 5 to 160 fold increase in HIV viral replication, which may decrease after successful TB treatment.

Pleural fluid from patients with tuberculosis increases HIV replication in activated lymphocytes and in HIV-infected patients with pulmonary tuberculosis, the concentrations of retroviral RNA in bronchoalveolar lavage fluid are highest in areas of tuberculous involvement[37].M.Tuberculosis probably increases HIV replication by inducing macrophages to produce tumor necrosis factor α, interleukin-1 and interleukin-6 [38,39].

CLINICAL MANIFESTATIONS OF TB IN HIV:

Unlike other opportunistic infections, TB can occur in persons with early –stage HIV infection (CD4 count >300/cubic mm). Clinical and radiological manifestations of TB are similar to those seen in non HIV infected persons [(37,40)].

Children are less likely to present with extrapulmonary disease at this stage of HIV infection. Because of the increased virulence in immunocompetent hosts of M.Tuberculosis compared with other opportunistic infections, tuberculosis can occur early in the course of HIV infection. In several studies of HIV infected children with pulmonary tuberculosis, the median CD4 T-cell count was >300 cells/cubic mm.

Studies have shown that 88-92% of HIV infected persons with TB had only pulmonary involvement, whereas 0.6to3%had both pulmonary and extrapulmonary and 8to12% had only extrapulmonary involvement[37]. Of those with extrapulmonary involvement 85% had lymphadenopathy (mainly cervical) [37].

Miliary tuberculosis was uncommon and found in only 1.7% of HIV children with TB[37]. Though many HIV infected patients have typical clinical and radiological manifestations of tuberculosis, atypical presentations do occur frequently, especially in those with low CD4 counts. Thus cavitatory upper lobe tuberculosis is more common with those with CD4 counts >200/cubic mm, whereas hilar/mediastinal

adenopathy and diffuse pulmonary infiltrates (without cavitation) are more common in those with CD4 counts <200/cubic mm.

Typical symptoms include fever weight loss, cough of several weeks duration and failure of pulmonary signs and symptoms to subside despite adequate antibiotic therapy. Chest radiographs demonstrate the presence of lobar infiltrates with or without hilar adenopathy and diffuse infiltrates.In children with advanced HIV disease, TB may present atypical and common extrapulmonary manifestations were lymphadenopathy, pleural effusion, TB abdomen, TB meningitis and miliary tuberculosis[42].

The clinical feature of TB meningitis in children who are seropositive for HIV are not siginificantly different from those in seronegative children. However ventriculomegaly, gyral enhancement and cortical atrophy on CT scan are more common in HIV seropositive children[43]. Also,mortality and the incidence of severe neurological sequelae are more common in HIV seropositive children. Co-existing HIV encephalopathy and diminished immune function may account for poorer prognosis[43].

RADIOGRAPHIC FINDINGS:

The chest radiograph is the cornerstone of diagnosis for pulmonary tuberculosis. Upper lobe infiltrates and cavities are the typical findings in reactivation tuberculosis, whereas intrathoracic lymphadenopathy and lower lobe disease are seen in primary tuberculosis. In HIV-infected children with CD4 T cell counts >200/ cubic mm the radiographic pattern tends to be one of the reactivation disease with upper lobe infiltrates with or without cavities.

In HIV-infected persons with a greater degree of immunosuppression (e.g. CD4 T-cell count < 200 cells/mm^3) hilar/mediastinal lymphadenopathy and lower lobe infiltrates are common [41]. As chest radiographs may appear normal in 7-14% of cases, a high index of suspicion must be maintained in evaluating an HIV-infected patient with symptoms suggestive of TB. The finding of low density lymph nodes with peripheral enhancement on a contrast-enhanced chest computed tomography (CT) scan is highly predictive of tuberculosis. Cavitation is unusual at advanced stage of immunosuppression, and infiltrates more often are diffuse or interstitial.

DIAGNOSIS

In children the majority of tuberculosis cases are diagnosed clinically without microbiological confirmation. The diagnosis is based mainly on clinical suspicion and radiological manifestation. In children with TB and HIV, special consideration is required in assessing results of tuberculin skin test and Acid-fast bacillus smear and culture.

TUBERCULIN SKIN TEST

HIV infection causes depression of cell mediated immunity, which can reduce the sensitivity and reliability of the tuberculin skin test. The TST is often negative, especially in those with more advanced HIV disease. Only one-third to less than half of children co-infected with TB and HIV have a positive tuberculin test [42,44,45] . Because of the higher risk of tuberculosis in children living in households with HIV-infected adults and because of diminished immune responses in children with HIV infection, the American Academy of Pediatrics recommends using induration ≥5mm as the criterion for diagnosis of tuberculous infection[46]. These criteria have not been adequately evaluated in developing countries, especially in those where BCG vaccination is a part of routine childhood immunization.

Although a positive result increases the likelihood of TB, a negative result does not exclude the diagnosis. Therefore diagnosis evaluation for TB should be undertaken in all children with clinical feature compatible with TB, regardless of the results of TB.

There are recent reports of restoration of delayed hypersensitivity on skin testing, including tuberculin skin testing in HIV-infected patients who begin highly active antiretroviral therapy. This reaction reflects restoration of the anti M-tuberculosis cell mediated immune response, a phenomenon that usually occurs within the first month of therapy.

Polymerase chain reaction and gene probes are approved for rapid identification of M.tuberculosis in sputum smears that are positive for acid-fast bacilli. These rapid tests are more sensitive than traditional staining methods but are not as sensitive as culture. Smears from extrapulmonary sites (e.g., bone marrow, lymph nodes) are often negative for acid-fast bacilli.

BACTERIOLOGICAL EXAMINATION

All patients suspected of having pulmonary tuberculosis should have 3 sputum specimens obtained on 3 consecutive days, and these specimens should be examined for AFB and cultured for mycobacteria. Contrary to what one would expect, smears and cultures are more often negative in HIV-infected adult patients with tuberculosis[47]. Similar findings are reported among children with co-infection[(42,44)].

In general the rate of smear positivity correlates with the extent of radiographic disease. For example, patients with cavitary lesions due to active tuberculosis will almost always have positive smears, whereas a negative smear in a patient with minimal disease on chest radiograph would not be unusual, and would not rule out active TB. However, in HIV infected patients positive smears may be seen with relatively little radiograph involvement. Despite this, it is recommended that aggressive attempts be made to obtain a positive culture to differentiate between M.tuberculosis and other mycobacteria, as well as to determine the antimicrobial susceptibility.

Smears from needle aspiration and Ziehl-Neelson staining are often negative in HIV patients who have tuberculous lymphadenitis[48].

Hence biopsy with histopathological examination and culture of lymph node tissue are recommended to establish the diagnosis.

Diagnostic tests for TB can be broadly divided into

1. Demonstration/isolation of Mycobacterium tuberculosis
2. Demonstration of host response to exposure to M.tuberculosis

(A) DEMONSTRATION OF M.TUBERCULOSIS OR ITS COMPONENTS

1. Ziehl-Neelson Staining
2. Special stains (Flurochrome stain, Auramine-O-stain etc.,)
3. Culture of mycobacterium tuberculosis
   - LJ medium
   - BACTEC radiometric assay
4. Polymerase chain reaction

(B) DEMONSTRATION OF HOST RESPONSE TO EXPOSURE TO M.TUBERCULOSIS

1. Serodiagnosis
2. Tuberculin skin testing

Newer diagnostic modalities including molecular methods of diagnosis of tuberculosis may yield better results than routine smear and culture in HIV infected population, but these methods need further evaluation. Moreover, these methods for diagnosis are seldom available in regions where the two infections most frequently co-exist.

DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION

Screening for latent tuberculous infection is an essential step in controlling the spread of tuberculosis. Screening for LTBI is recommended in persons at risk for recent infection and in those with increased risk of progression to active disease once infected, including HIV-infected persons.

The TST is currently the only method available for identifying LTBI. Routine annual TST is recommended in HIV infected individuals. A reaction of ≥5mm induration is considered positive for HIV infected patients and those with other forms of severe immunosuppression, person who are close contacts of infectious cases, and persons with abnormal radiographs consistent with tuberculosis. Use of 5mm cutoff is supported by a prospective study in the United States demonstrating that the risk of tuberculosis was significantly

higher in HIV-infected persons with TST≥5mm of induration than in those who have a reaction of <5mm [46].

Testing with tuberculin purified protein derivative is dependant on the presence of an intact cell mediated immune response. In the setting of HIV infection, reduced CMI can lead to decreased delayed-type hypersensitivity responsiveness, resulting in false-negative skin test. The prevalence of positive TST≥5mm was shown to decrease with decreasing CD4 T cell counts.

Application of multiple skin antigens (e.g. candida, mumps, tetanus toxoid etc.,) referred to as anergy testing, has been used to access cell-mediated immune function and to distinguish true negative from false negative tuberculin skin test results. In 1991, the CDC recommended that anergy testing be performed in conjunction with TST in HIV-infected persons based on the premise that anergic HIV-infected individual at high risk for tuberculosis infection would benefit from treatment with INH. In 1997, the CDC revised its recommendations and no longer recommends anergy testing while screening for M.tuberculosis infection in HIV-infected persons. The revised recommendation is based on the following points. First, there

are no standardized guideline for performing anergy skin testing. The appropriate number of control antigens to administer or the appropriate cut off for interpreting a test as positive in nor known. Second, the response to skin testing with control antigens as well with tuberculin can vary over time. Several studies have demonstrated that HIV-1 seropositive individuals can regain DTH responsiveness with time [49]. The only factor associated with regaining DTH responsiveness was the CD4-T cell count, the higher the CD4 count, the more likely the individual regains DTH responsiveness.

In some with tuberculous infection, DTH responsiveness may decrease with time. A second TST, applied weeks to month after the first, can boost the DTH response resulting in a positive skin test reaction. Such responses are considered true evidence of tuberculous infection.

NATURAL HISTORY

Although the immune response to M. tuberculosis is important in controlling disease, immune activation may also be associated with increased HIV viral load and accelerated progression of HIV infection. HIV-infected patients with tuberculosis do not survive as long as HIV

infected controls without tuberculosis, even after controlling for baseline CD4 T-cell count. When tuberculin positive HIV infected patients were given INH therapy, they were less likely to develop AIDS and less likely to die. Thus, it is likely that tuberculosis acts to accelerate the clinical course of HIV infection.

Although increased viral replication is thought to play a role, the mechanisms by which tuberculosis accelerates progression of HIV disease are not known with certainty. High levels of TNF-α which are known to increase HIV replication in T-cell clones, have been demonstrated in both HIV-1 seropositive and seronegative tuberculosis cases.

Moreover, investigators have shown that M. tuberculosis or purified protein derivative can also increase viral replication in infected T lymphocytes and monocytes [36].

TREATMENT

Standard treatment regimens:

Anti-TB therapy is equally effective in HIV negative and HIV positive patients. The weight of the evidence to date indicates that the rate of TB relapse after short-course (6-month rifampicin based)

therapy is similar for HIV-positive and HIV negative patients, although this remains somewhat controversial. In general the same treatment regimen may be used regardless of HIV status [49]. The American Thoracic Society TB treatment guidelines (currently under revision) will likely include a recommendation to extend the duration of therapy to 9 months (regardless of HIV status) in persons who have both cavitary pulmonary disease on initial presentation and positive-sputum cultures after 2 months of treatment. These changes are based on results of a recent TB-treatment study conducted by CDC, in which HIV negative adults with pulmonary disease who met these criteria had a relapse rate of >20% far higher than clinically acceptable relapse rate of <5% [49].

PULMONARY TUBERCULOSIS

For drug susceptible pulmonary TB standard 6 month therapy with isoniazid (INH), rifampicin (RIF) Pyrazinamide (PZA) and Ethambutol (EMB) daily for intitial two months followed by INH and RIF daily or twice weekly, for atleast four additional months is recommended. Conversion from sputum positive to sputum negative with this regimen is similar in HIV seropositive and seronegative patients with tuberculosis. However it is not known if relapse rates are

higher in HIV infected patients. Hence some experts recommend extending the treatment to 9 months in those who show slow response. Slow response is defined as sputum positivity or persistence of signs and symptoms of disease after 2 months of therapy. DOTS is recommended wherever possible [49].

EXTRAPULMONARY TUBERCULOSIS

The drug regimen and duration of treatment used for pulmonary tuberculosis are generally adequate to treat most forms of extrapulmonary tuberculosis. However, for certain forms of tuberculosis such as meningitis and bone and joint tuberculosis, a 9 month regimen of rifamycin containing regimen is recommended[49].

DRUG RESISTANT TUBERCULOSIS

The risk of drug resistant tuberculosis is higher among those co-infected with HIV[50]. The reasons for this is not clear, but this might reflect the fact that a higher proportion of tuberculosis disease in HIV infected individuals follows recently acquired infection.

In recent years there had been an increasing number of reports of rifampicin monoresistance in HIV co-infected patients. The reasons for

this is not fully understood. Possible reasons include (1) increased rates of bacterial replication in an environment of suppressed CMI. (2) selective drug malabsorption and (3) inadequate tissue penetration of the drug.

For isoniazid-resistant tuberculosis, a regimen containing Rifamycin, Pyrazinamide and Ethambutol may be used for the full duration of treatment 6-9 months. Intermittent therapy may be used after daily therapy for the initial 8 weeks.

For tuberculosis resistant only to rifampicin a 9 month regime consisting of INH, EMB, PZA and streptomycin for the initial two months, followed by INH, PZA and streptomycin, for the next 7 months is recommended.

In multidrug resistant tuberculosis resistant to INH and RIF, aggressive treatment with a regime that contains an aminoglycoside or capreomycin and a fluroquinolone is recommended. The duration of therapy must be at least 24 months after culture conversion.

PHARMACOKINETIC INTERACTION

A central aspect of TB treatment in HIV infected patients is the pharmacokinetic interactions between rifamycins and PI and NNRTI'S. Although these interactions do not preclude the concomitant use of potent antireteroviral therapy and anti TB therapy clinicians must be aware of these interactions and adjust dosages accordingly. Although large studies of the effectiveness of rifabutin based regimens in co-infected patients concomitantly receiving antireteroviral therapy are underway, the results will not be available for 1 to 2 years.

Rifampicin induces the enzyme CPY450 that increases the metabolism of protease inhibitors resulting in lower serum levels of these drugs [49]. Since PI resistant mutants of HIV may emerge if optimal levels of the drug are not maintained during therapy concomitant therapy with rifampicin and PI's is not recommended.

On the other hand the protease inhibitor ritonavir inhibits CPY450, which results in increased concentration of rifabutin and resultant toxicity. Since current evidence indicates that the anti-tuberculosis activity of rifabutin is equal to that of rifampicin, it is not recommended that this drug be used instead of rifampicin in the

treatment of TB in patients receiving PI's, the PI ritonavir should not however, be used in treatment regimens containing rifabutin.

DIRECTLY OBSERVED THERAPY

DOT is becoming the standard of care of TB [51, 52]. A large body of evidence has conclusively proven that a large proportion of patients do not take medications regularly as prescribed and that it is not possible to predict which patients will not adhere to treatment. Surprise home visits as per studies from Tuberculosis Research Centre, Chennai showed a much greater degree of non-adherence than pill counts or urine tests [53].

The efficacy of short-course intermittent treatment has been conclusively demonstrated in controlled clinical trials in India and elsewhere [54]. Short course treatment has been documented to be effective for extrapulmonary TB. Since the doubling time of M.tuberculosis is 18-24 hours, compared with 12-20 minutes for most bacteria intermittent therapy given twice or thrice weekly is as effective as daily therapy [55]. Among HIV infected children, directly observed therapy has been associated with improved survival. Because

of these benefits, DOT therapy is recommended by the American Thoracic Society, the CDC and WHO [51].

WHO recommended Treatment regimen

Category of treatment	Type of patients	Regimen	
		Initial phase	Continuation phase
Category I	New sputum smear positive PTB, New sputum negative PTB with extensive parenchymal involvement. New cases of severe forms of extrapulmonary TB	2H3R3Z3E3	4H3R3
Category II	Sputum smear-positive relapse, Treatment failure Treatment after default	2H3R3Z3E3S3 / 1H3R3Z3E3	5H3R3E3
Category III	New smear negative and extrapulmonary, not seriously ill	2H3R3Z3	4H3R3

Sputum examined after 2 months for patients for Category I and after 3 months for patients in Category II [26]. All treatment thrice weekly. Category I and Category II extended one month if smear

positive at end of initial intensive phase. H-Isoniazid, R-Rifampicin, Z-Pyrazinamide, E-Ethambutol, S-Streptomycin.

HIV AND PARADOXICAL REACTION TO TREATMENT

Patients who receive anti-tuberculosis treatment along with anti-retroviral therapy may manifest a paradoxical worsening of symptoms, which are attributable to a recovery of tuberculin hypersensitivity as a result of therapy[56]. Such patients manifest with hectic fever, lymphadenopathy, worsening of chest radiographic findings (miliary infiltrates and pleural effusion) and worsening of original tuberculosis lesions. Paradoxical worsening is thought to represent an improvement of the host's immune response to mycobacterial antigens during the course of treatment leading to more intense inflammation at sites of TB disease.

The course of paradoxical worsening can be brief or prolonged with multiple exacerbations and recurrences. Discontinuation or changes in tuberculosis or antiretroviral therapy is rarely required in most situations. A short course of steroids to suppress the immune response may ameliorate some of the signs and symptoms, such as lymphadenopathy.

TREATMENT OF LATENT TB INFECTION

The risk of progressing to active TB is high among HIV seropositive persons infected with M.tuberculosis. Therefore all HIV-infected children with evidence of latent M.tuberculosis should receive treatment as the WHO recommends treating latent TB infection. Despite strong evidence supporting the rationale of INH preventive therapy in latent TB infection, implementation of IPT has not been widespread in countries with high TB burden. This is due to recurring concerns over drug resistance, short course of IPT efficacy and difficulties in ruling out active TB in populations with high HIV prevalence with limited diagnostic tools available.

WHO recommendations for the treatment of HIV and TB co-infection with reference to CD_4 cell count

CD4 cell count	Recommended regimen	Comments
<200 mm³	Start TB treatment. Start ART as soon as TB treatment is tolerated (2 weeks to 2 months). EFV containing regimens	Recommended ART
200 to 350 mm³	Start TB treatment. Start one of the below regimens after initiation phase. EFV containing regimens or NVP regimens in case of rifampicin free continuation phase TB treatment regimen	Consider ART
>350 mm³	Start TB treatment	Defer ART
CD4 count not available	Start TB treatment	Consider ART

BCG VACCINATION

There are a few case reports of disseminated BCG infection in individuals with HIV. However several studies in developing countries have documented that adverse reactions following BCG vaccination in HIV infants are no higher than in non-infected infants [57]. Therefore

BCG vaccination is recommended for infants of HIV infected mothers in countries where it is a part of routine immunization schedule, provided the children do not have evidence of advanced immunodeficiency. However the efficacy of BCG in HIV infected children is not known. One small case control study showed no efficacy in HIV infected children compared to 59% efficacy in uninfected children of HIV seropositive mothers [58].

BACKGROUND OF THE STUDY

Tuberculosis is a life threatening, transmissible and pandemic disease, especially among HIV infected patients. In developing countries like India, where HIV infection is becoming prevalent and where TB infection has long been endemic, the incidence is increasing.

HIV infected children are at increased risk of developing tuberculosis due to depressed cell mediated immunity.

This study is aimed to identify the prevalence and the clinical profile of TB in HIV seropositive children in our region, which will help in early diagnosis and management.

MATERIALS AND METHODS

Nature of the study: Descriptive study

Study population : 100 children screened positive for HIV at VCTC in ART centre, and diagnosed to have TB infection as per RNTCP guidelines at GMKMCH Salem.

Period and place of study: This study was conducted over a period of 12 months from May 2008- April 2009 at GMKMCH Salem.

Inclusion criteria:

- Children who are seropositive in the age group of 18 months to 12 years registered in the ART centre.
- Children with stigmata for TB like fever, cough with expectoration lasting for more than three weeks, loss of appetite and loss of weight.
- Children who are suffering from Extra pulmonary TB infection like TB pericarditis, TB Meningitis, TB Abdomen, Isolated TB Potts spine, Disseminated TB.

EXCLUSION CRITERIA:

Children < 18 months were not taken into consideration, as the facility for making diagnosis of HIV by PCR was not available in our centre.

PROFORMA

A special proforma was designed to record the following information.

- Demo graphic data
- History at presentation
- Clinical findings
- Nutritional status
- Developmental history
- Parental and sibling status
- Mode of transmission
- Socio economic history
- Stage of the disease
- Immunisation history

Informed consent was obtained from the parent/ guardian for registering the required data. The seropositive children were subjected to the following further investigation that include,

- Blood hemoglobin
- Total count
- Differential count
- Erythrocyte sedimentation ratio
- Liver function test
- Sputum for AFB/ Resting gastic juice analysis
- Mantoux test
- Chest x-ray PA view/ AP view
- CD4 count / CD4 %
- FNAC
- USG Abdomen
- C T scan brain
- CSF
- Others (x-ray spine) etc.

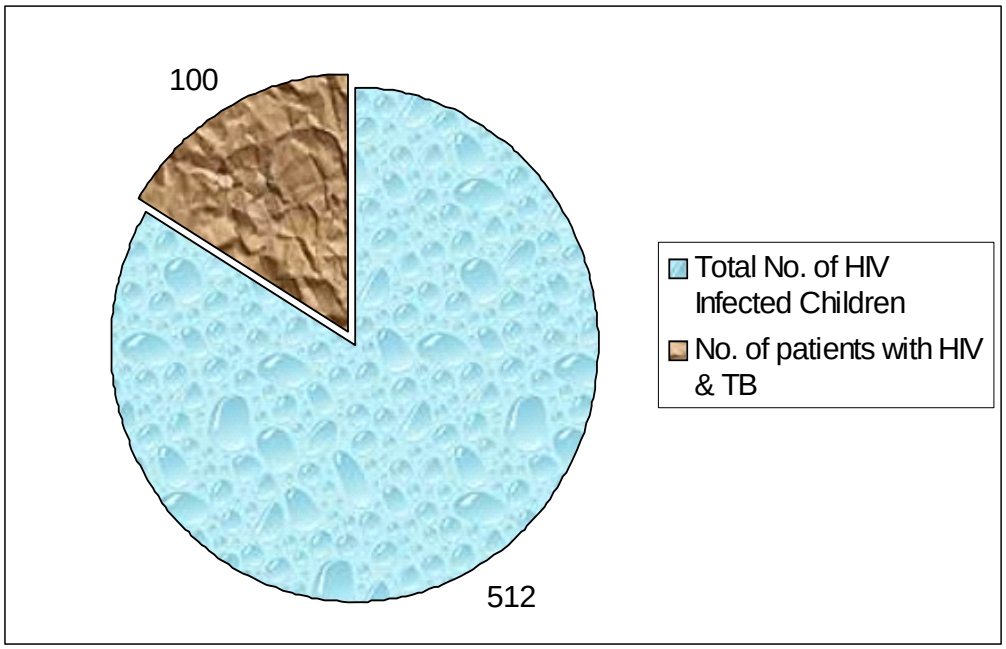
STUDY LIMITATIONS

The confirmation of HIV infection could not be done by Western Blot analysis. The sputum positivity for tuberculosis infection in HIV infected children is low. Hence for confirmation of Tuberculosis infection in these seropositive individuals, sputum culture must be done which could not be done in our study.

OBSERVATION & RESULTS

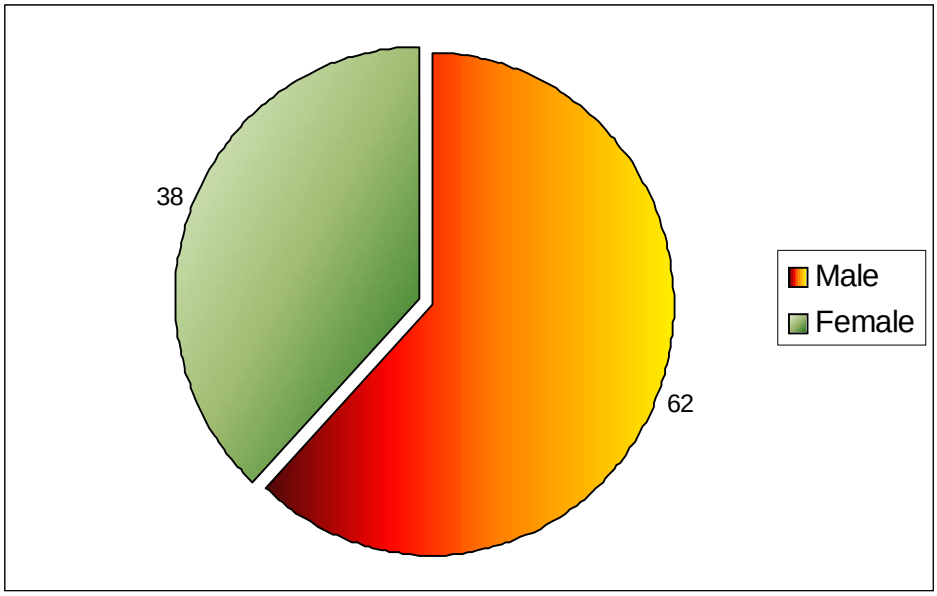
The study population was derived from the persons attending outpatient department at GMKMCH, Salem. Out of 512 confirmed cases of HIV infection, 100 were found to be suffering from Tuberculosis, they formed the study population.

The prevalence of tuberculosis in HIV infected children was 19.53%.



SEXWISE DISTRIBUTION

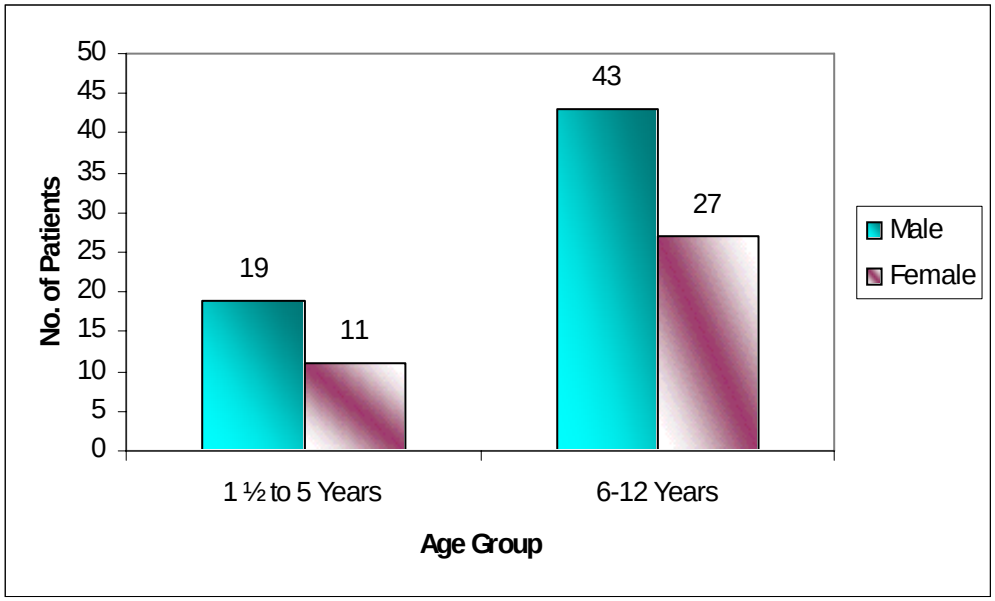
Out of the 100 children with HIV and TB infection 62 were males and 38 were females. The ratio was 1.63:1.



AGEWISE DISTRIBUTION

The age-wise distribution of cases were as follows

Age group	Male	Female
1 ½ to 5 Years	19	11
6-12 Years	43	27
Total	62	38

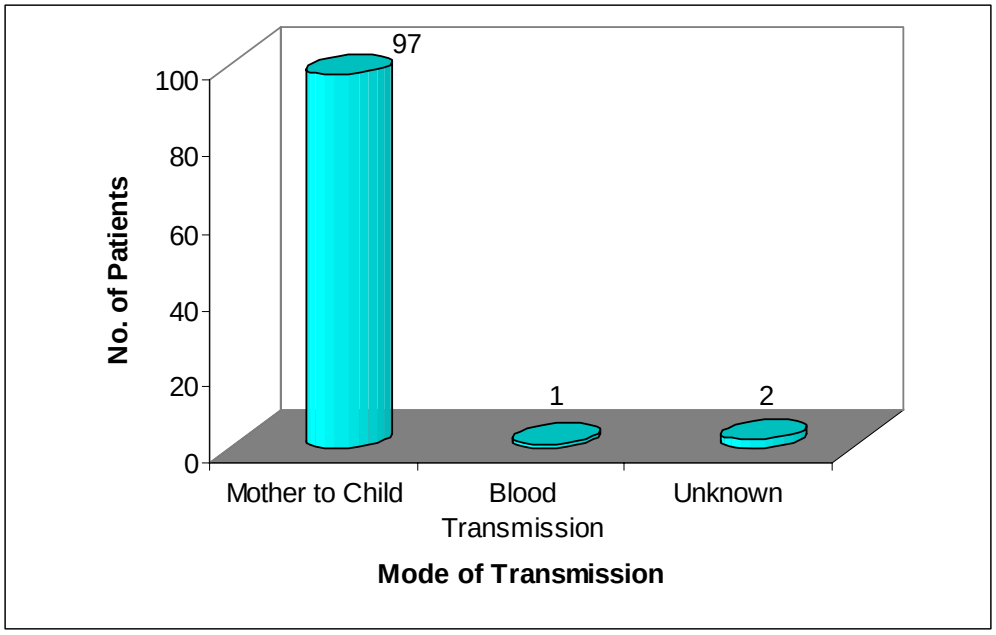


MODE OF TRANSMISSION

Mother to child transmission accounted for the highest route of transmission (97%).

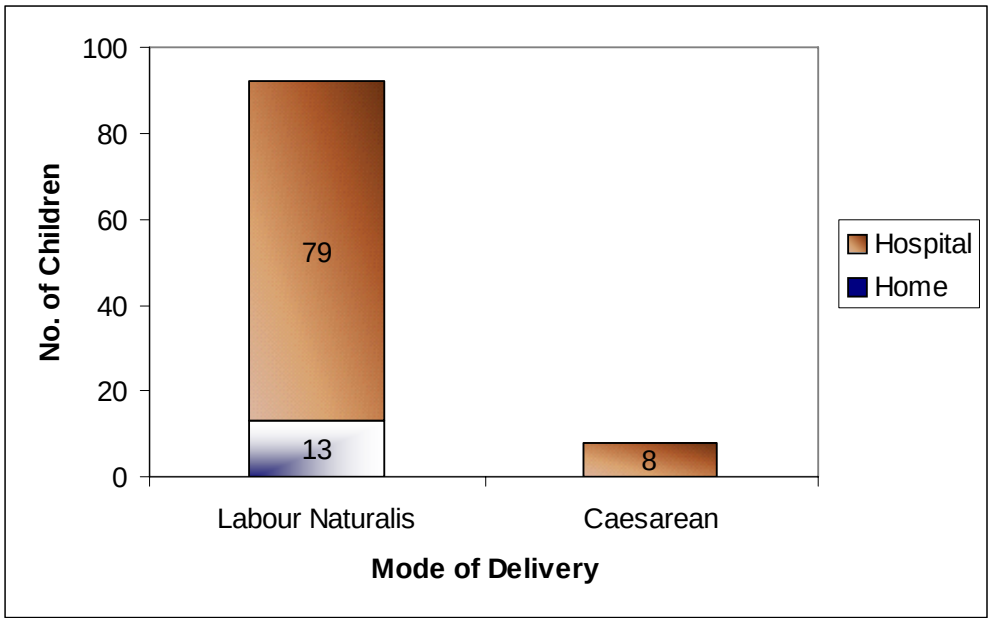
In two children the actual mode of transmission could not be identified (2%)

One child was most likely affected due to Blood transfusion given during acute illness (1%)



PLACE AND MODE OF DELIVERY

92 Children were delivered by normal vaginal delivery out of which 13 were delivered at home, rest 79 were delivered in hospital. 8 Children were delivered by emergency LSCS.

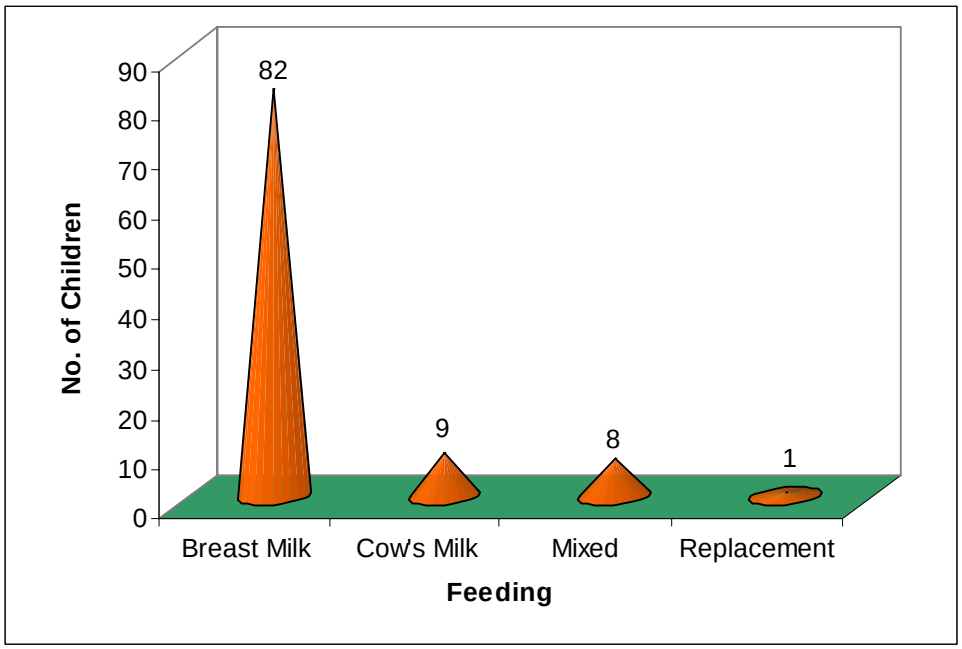


NEVIRAPINE/HAART THERAPY DURING ANTENATAL PERIOD

Out of 100 children only 2 children received Nevirapine during the Peripartum period. None of the mothers received HAART during Antenatal period.

FEEDING

82 Children received breast milk for the initial 4 months. 9 children received cow's milk and 8 children received both cow's milk and breast milk. Only one child was completely replaced with milk substitute.



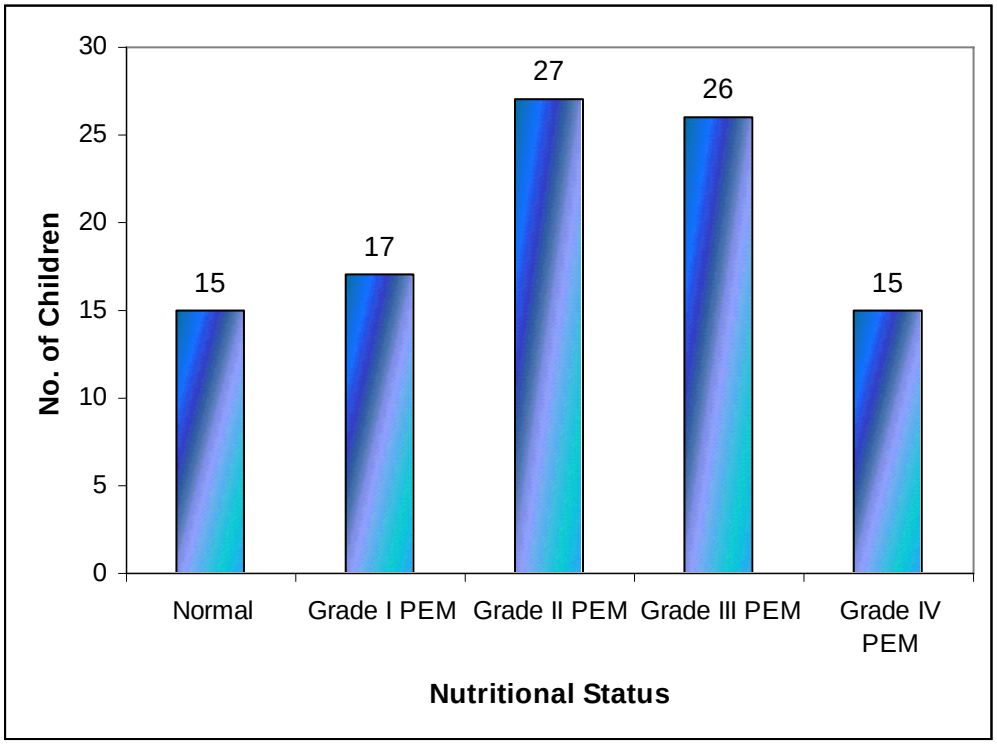
DEVELOPMENTAL HISTORY

98 Children presented with normal developmental history only 2 children had delayed motor milestones.

NUTRITIONAL STATUS

The nutritional status of the children was classified as per IAP classification of malnutrition as follows.

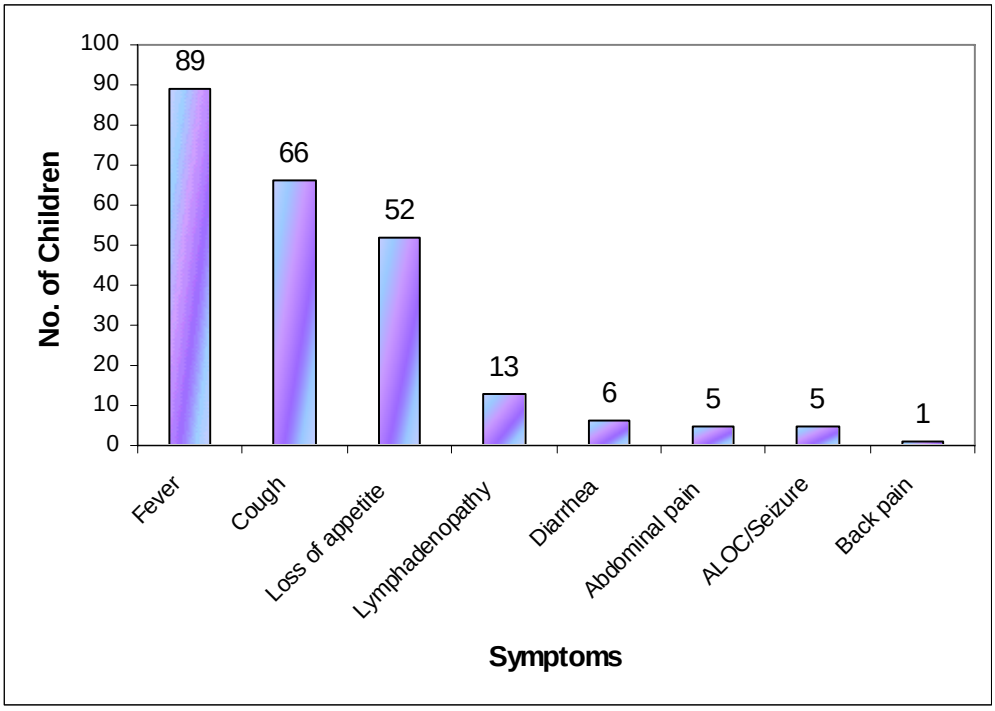
Nutritional Status*	Weight for age (% of expected)	No. of Children
Normal	> 80	15
Grade I PEM	71-80	17
Grade II PEM	61-70	27
Grade III PEM	51-60	26
Grade IV PEM	< 50	15



SYMPTOMS

The common symptoms present in the study group was as follows:

Fever	- 89%
Cough	- 66%
Loss of appetite	- 52%
Lymphadenopathy	- 13%
Diarrhea	- 6%
Abdominal pain	- 5%
ALOC/Seizure	- 5%
Back pain	- 1%



SYSTEM EXAMINATION

The clinical presentations was Lymphadenopathy mostly cervical (11%) and axillary in 1%. In respiratory system signs of pneumonia was present in 60%, 2 children had pleural effusion, 2 had bronchiectasis, 2 children had consolidation/collapse. Thus respiratory system was involved in 66% of children.

Gastrointestinal system (9%) 5 children presented with hepatomegaly, 5 children presented with hepatosplenomegaly and 4 children had ascites.

Oral lesion (24%) 14 children had Oral candidiasis, 4 children had Apthous ulcers, 3 children had Angular stomatitis and 3 children had Herpes simplex.

Skin Lesions (15%) 6 children had Herpes zoster, 4 children had Molluscum contagiosum, 2 children had scabies, 2 had extensive impetigo and 1 child had rash.

Central Nervous System (7%) Meningitis are present in 7 children out of which 1 child had Cranial nerve involvement.

Spinal involvement was present in 1 child (Pott's spine).

SYSTEM INVOLVEMENT	PRESENTATION
Respiratory System (66%)	Pneumonia – 60% Pleural Effusion – 2% Bronchiectasis – 2% Consolidation/Collapse -2%
Gastrointestinal system (9%)	Hepatomegaly – 5% Hepatosplenomegaly – 5% Ascites – 4%
Lymphadenopathy (12%)	Cervical – 11% Axillary – 1%
Oral lesion (24%)	Oral candidiasis – 14% Apthous ulcers – 4% Angular stomatitis – 3% Herpes simplex – 3%
Skin Lesions (15%)	Herpes zoster-6% Molluscum contagiosum-4% Scabies-2% Extensive impetigo-2% Rash-1%
Central Nervous System (7%)	Meningitis -7% Cranial nerve involvement -1%
Spinal involvement (1%)	Pott's spine – 1%

EXTRAPULMONARY MANIFESTATIONS:

26 Children had extrapulmonary system involvement:

Lymphadenopathy - 13

TB Meningitis - 6

TB abdomen - 4

Disseminated TB - 2

TB Spine - 1

SPUTUM POSITIVITY

Sputum for AFB	Number
Sputum Positive	9
Sputum Negative	91

CORRELATION BETWEEN SPUTUM POSITIVITY AND CD4 COUNT

CD4 count	Sputum Positive	Sputum Negative
0-100	1	13
101-200	-	7
201-300	1	11
>300	7	60
Total	9	91

MANTOUX TEST

Mantoux testing was done in 25 children who were admitted in our hospital, out of which only one child was mantoux positive.

Mantoux reading	Number
0-4 mm	2
5-9 mm	-
10-14 mm	1

CD4 CELL COUNT

The CD4 cell count was as follows:

CD4 cell count/mm^3	Number
0-100	14
101-200	7
201-300	12
>300	67

WHO CLINICAL STAGING

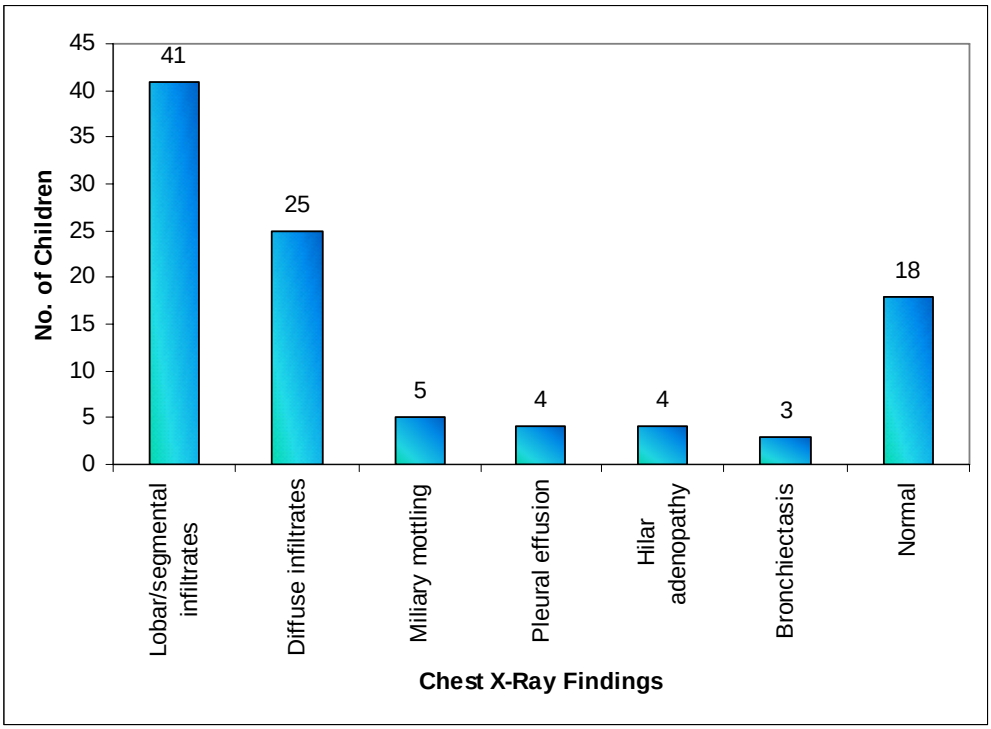
WHO STAGE	NUMBER
Stage III	87
Stage IV	13
TOTAL	100

The CD4 count correlation with WHO clinical staging was as follows:

CD4 COUNT	WHO STAGE	
	STAGE III	STAGE IV
0-100	9	5
101-200	6	2
201-300	12	2
>300	59	5
Total	86	14

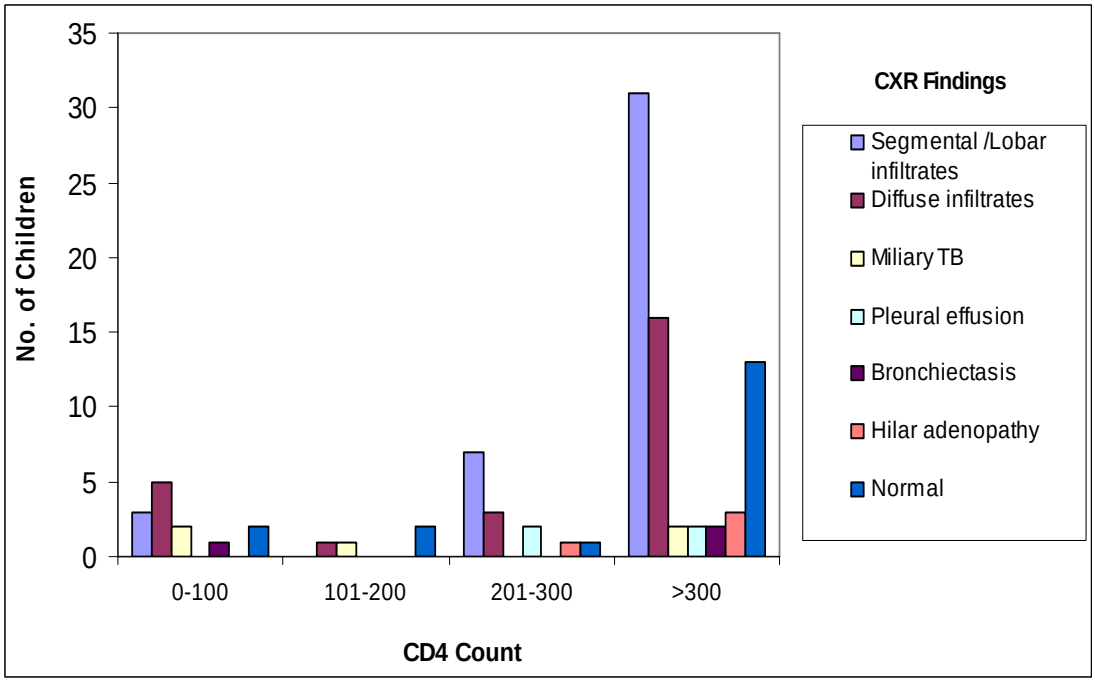
CHEST X-RAY FINDINGS

CHEST X-RAY FINDINGS	NUMBER
Lobar/segmental infiltrates	41
Diffuse infiltrates	25
Miliary mottling	5
Pleural effusion	4
Hilar adenopathy	4
Bronchiectasis	3
Normal	18
Total	100



The correlation of CXR findings with CD4 count:

CD4 Count	Segmental /Lobar infiltrates	Diffuse infiltrates	Miliary TB	Pleural effusion	Bronch-iectasis	Hilar adenopathy	Normal
0-100	3	5	2	-	1	-	2
101-200	-	1	1	-	-	-	2
201-300	7	3	-	2	-	1	1
>300	31	16	2	2	2	3	13
Total	41	25	5	4	3	4	18



DISCUSSION

Among the 512 patients infected with HIV infection, 100 children were having TB co-infection, with a prevalence of 19.53%. This corresponds to other studies like **Merchant et al** [59] where 29.5% were co-infected. **Lodha et al** [60] (59.1%) and **Dhurat et al** [61] (67.5%) have also recorded the increased prevalence of HIV-TB co-infection.

Out of 100 seropositive children with TB co-infection, 62% were males and 38% were females. This indicates that the male:female ratio is 1.6:1. The prevalence of HIB-TB co-infection is 70% in the age group of 6-12 years. This correlates well with the observations of **Shahab, Afzal et al** [62] where the male:female ratio was 2.3:1 and prevalence of coinfection was 72.4% in the age group of 1-9 years.

History of contact with TB was present in 38% as against 47% in the results of **Shahab, Afzal et al** [62] . 73% of the children in our study population were taken care by their parents (father 55% and mother 18%) rest 27% were orphaned and taken care by their grand parents.

97 Children acquired infection by perinatal transmission, one child has infected following blood transfusion. In two children the

actual mode of transmission could not be identified. **Verghese VP, Cherian et al**[63] study reported that perinatal transmission was the predominant root of transmission (87%) followed by blood transfusion (10%) and the mode of transmission could not be ascertained in rest 3%. Blood and blood products remain an important source of infection in 10-30% of total cases in developing countries[60].

The children in stage IV were severely malnourished and belonged to Grade III & Grade IV PEM. All children in our study population were on regular Cotrimoxazole prophylaxis.

Analysis of the clinical manifestations of TB in seropositive children

Fever was the most common clinical manifestation followed by cough and loss of appetite.

Symptom	Our study	Shahab, Afzal et al [62]
Fever	89%	87.6%
Cough	66%	41.2%
Loss of appetite	52%	48.5%
Lymphadenopathy	13%	23%
Abdominal pain	5%	1%
Diarrhea	6%	1%
Neurological (ALOC/seizures)	5%	9%
Others (Back pain)	1%	-

Systemic examination revealed respiratory system findings and Lymphadenopathy were present in 66% and 12% respectively. About 9% had hepatomegaly/hepatosplenomegaly with ascites in 4% of the children. 24% of children presented with oral lesions(mostly oral candidiasis 14%) and skin lesions was present in 15%.

General/system examination	**Our study**	**Shahab, Afzal et al [62]**
Respiratory system findings	66%	36.5%
Lymphadenopathy	13%	28%
Hepatomegaly	5%	-
Hepatosplenomegaly	4%	11.5%
Skin lesions	15%	3%
Oral candidiasis	14%	30%
CNS involvement	7%	5%

Extrapulmonary TB was seen in 26% of children in our study which includes Lymphadenopathy 13%, TB Meningitis 6%, TB abdomen 4%, Disseminated TB 2% and TB spine 1%. This finding corresponds to the earlier observations of **Dhurat et al**[61] and **Merchant et al**[59].

The sputum positivity in our study shows that only 9% of the children are sputum positive. Sputum culture for M.Tuberculosis

remains the gold standard for the diagnosis of Pulmonary TB. In resource poor countries the diagnosis is heavily dependent on the sputum AFB smear. HIV infected children have reported to have a lower yield on AFB smears as observed in **Mukadi et al**[42], **Garay JE et al**[44]. **Verghese VP et al**[63], reported only 4% smear positive cases in HIV children.

In our study Mantoux was done in 25 children who were admitted in our hospital and only one child was Mantoux positive with more than 10 mm induration. This correlates well with study by **Mukadi et al**[42] which shows an increased incidence of anergy in HIV infected and AIDS patients.

In our study CD4 cell count less than 300 was observed in 33 children. In these children the predominant X-ray lesions were Hilar adenopathy, lower lobe infiltrations, diffuse infiltrates and miliary mottling. Upper lobe infiltrates was common with higher CD4 count mean 350. These finding correlates well with **Verghese VP et al**[63] and **Shahab, Afzal et al** [62].

The most important finding of this study is the impact of HIV related immunosuppression among children with TB. 8 children with CD4 % of less than 10% died during 6 months of therapy. This finding correlates well with the study of **Mukadi et al**[42]

CONCLUSION

- Tuberculosis is a common opportunistic infection among HIV seropositive individuals.
- Males are commonly affected than females.
- Tuberculosis occurs early in HIV infection even before CD4 count falls to very low levels.
- Fever, cough, loss of appetite and loss of weight are the most common symptoms observed in HIV-TB co-infection.
- Extrapulmonary TB is present in 30% of HIV seropositive children.
- Sputum negativity was more commonly seen in TB of HIV seropositive individuals.
- Mantoux anergy was observed with lower CD4 counts.
- This study documents the importance of HIV infection as an independent risk factor for the development of TB in children and also demonstrate that HIV related immunosuppression as critical risk factor for mortality in this population.
- With the conventional sputum positivity and Tuberculin test not providing an adequate diagnostic help, familiarity with clinico radiological spectrum of TB and HIV co-infection will help in early diagnosis and improve survival among HIV seropositive children.

MASTER CHART

Sl. No.	Age (yrs.)	Sex (M/F)	Weight (kg.)	Mode of Transmission	ANC	POD/MOD	Feeding	Contact History	Socio-Economic Status	Clinical Features	System Examination	Sputum for AFB	MTX	CXR	CD4 Count	FNAC	USG Abdomen	CT Scan, CSF, Others	WHO Stage	ATT	CAT	Rx Outcome	Ctx
1	12	M	17	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	UZ	577 (17%)	-	-	-	III	P	I	C	✓
2	9	F	16	MTC	-	I/CS	BF	-	↓	1,6	VII	-	-	LZ	89 (10%)	-	-	CS	IV	EP	I	C	✓
3	7	M	17	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	LZ	374 (14%)	-	-	-	III	P	I	C	✓
4	4 1/2	F	14.5	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	UZ	693 (19%)	-	-	-	III	P	I	T	✓
5	10	M	11	MTC	-	I/LN	BF	+	↓	4	I	-	-	LZ	283 (9%)	+	-	-	III	EP	II	DE	✓
6	12	M	25	MTC	-	I/LN	BF	+	↓	1,3,6	VI	-	-	LZ	28 (5%)	-	-	CSF+	IV	EP	I	D	✓
7	7	F	17	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	LZ	777 (11%)	-	-	-	III	P	I	C	✓
8	6	M	15	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	M	98 (4%)	-	-	-	III	P	I	C	✓
9	4	F	14.5	MTC	NVP	I/LN	CM	-	↓	2,3, 5,6	IV, V	-	+	PE	1070 (16%)	-	HSM, PE, A	-	III	EP	I	C	✓
10	11	F	20	MTC	-	I/LN	BF	-	↓	1,2,5	V	-	-	B	671 (11%)	-	HEP, A, N	-	IV	EP	I	C	✓
11	9	M	18	MTC	-	I/LN	Mix	-	↓	1,2,6	IV, V	-	-	DI	81 (4%)	-	HEP, A	CT Chest, B	IV	EP	I	C	✓
12	3 1/2	M	10	MTC	-	I/LN	Mix	+	↓	1,2	IV	-	-	DI	889 (13%)	-	HEP	-	III	P	I	C	✓
13	5	F	11	MTC	-	I/LN	BF	-	↓	1,2	IV, V	-	-	B	282 (10%)	-	HSM	-	III	P	I	C	✓

14	11 1/2	M	13	MTC	-	I/LN	BF	-	↓	1,2,6	II, V	-	-	LZ	680 (15%)	-	-	CT Norm	III	P	I	C	✓
15	11	M	19.6	MTC	-	H/LN	BF	-	↓	1,2	V	-	-	DI	82 (8%)	-	-	-	III	P	I	C	✓
16	12	M	20	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	LZ	356 (26%)	-	-	-	III	P	I	C	✓
17	9	M	17	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	LZ	188 (16%)	-	-	-	III	P	I	C	✓
18	8	M	18.6	MTC	-	I/LN	Mix	-	↓	4	I, IV	-	-	UZ	604 (15%)	+	-	-	III	P	I, II	T	✓
19	11	M	20	MTC	-	H/LN	BF	-	↓	1,2,5	II, IV	-	-	LZ	252 (12%)	-	Norm	-	III	P	I	C	✓
20	9	M	18	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	LZ, MZ	1024 (12%)	-	-	-	III	P	I	C	✓
21	10	M	18	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	LZ	89 (3%)	-	-	-	III	P	I	C	✓
22	4	M	10	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	LZ	206 (11%)	-	-	-	III	P	I	D	✓
23	4	F	15	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	LZ	773 (15%)	-	-	-	III	P	I	C	✓
24	9	F	18	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	LZ	656 (11%)	-	-	-	III	P	I	C	✓
25	11	F	20	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	M	805 (25%)	-	-	-	III	P, EP	II	C	✓
26	12	F	29	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	LZ	269 (12%)	-	-	-	III	P	I	T	✓
27	6	M	12	MTC	-	I/LN	BF	+	↓	1,2, 3,4	I, II	-	-	-	294 (13%)	+	-	-	III	EP	I	C	✓
28	11	M	24	MTC	-	I/LN	BF	-	↓	1,3	II, V	-	-	-	16 (3%)	-	HEP	CT +	IV	EP	I	D	✓
29	9	M	18	MTC	-	H/LN	BF	+	↓	1,2, 3,4	I, II	-	-	-	1019 (37%)	+	-	-	III	EP	I	C	✓
30	3	F	10	MTC	-	I/LN	BF	-	↓	1,2,3	II, IV	+	-	LZ	853 (17%)	-	HSM	-	III	P	I	C	✓

31	2	M	11	MTC	NVP	I/LN	Mix	-	↓	4	I	-	-	-	858 (15%)	+	-	-	III	EP	I	C	✓
32	6	M	12	MTC	-	I/LN	CM	+	↓	1,4	I	-	-	-	618 (20%)	+	-	-	III	EP	I	C	✓
33	3	M	9	MTC	-	I/LN	BF	-	↓	1,3,5	IV, VI	-	-	M	582 (16%)	-	-	CT +, CSF +	IV	P, EP	I, II	C	✓
34	7	M	10	MTC	-	I/LN	BF	+	↓	1,6	VI	-	-	-	1278 (28%)	-	-	CSF+	IV	EP	I	T	✓
35	5	M	15	UK	-	H/LN	BF	-	↓	1,4	I, III	-	-	-	1312 (30%)	+	-	-	III	EP	I	C	✓
36	12	F	22	BT	-	I/LN	BF	-	↓	1,2,3	IV	-	-	HA	287 (7%)	-	-	-	III	P	I	C	✓
37	5	MF	15	MTC	-	I/LN	BF	-	↓	1,3,5	III, IV	-	-	DI	18 (4%)	-	HEP, N	-	III	EP	I	D	✓
38	6	M	9.7	MTC	-	I/LN	Mix	+	↓	1,2,3	IV	-	-	DI	71 (12%)	-	-	-	III	P	I	D	✓
39	11	M	17	MTC	-	I/LN	BF	-	↓	1,2,3	II, III	-	-	PE	777 (23%)	-	-	-	III	P	I	IR	✓
40	7	M	14.2	MTC	-	I/LN	BF	+	↓	4	I, III	-	-	-	671 (10%)	+	-	-	III	EP	I	C	✓
41	9	F	16	MTC	-	I/LCS	Mix	+	↓	1,2, 3,4	IV	+	-	LZ, MZ	1017 (21%)	-	-	-	III	P	I	C	✓
42	10	F	25	MTC	-	I/LN	BF	-	↓	1,2,3	III	+	-	LZ	556 (23%)	-	-	-	III	P	I	C	✓
43	4	M	11	MTC	-	I/LN	BF	-	↓	1,2,3	III	+	-	HA	612 (15%)	-	-	-	III	P	I	C	✓
44	5	M	15	MTC	-	I/LN	BF	-	↓	1,2,3	III	-	-	-	227 (6%)	-	-	CT+	IV	P	I	C	✓
45	8	M	16	MTC	-	I/LN	CM	-	↓	1,2,3	IV	-	-	DI	410 (11%)	-	-	-	III	P	I	C	✓
46	7	M	16	MTC	-	I/LN	BF	-	↓	1,2, 3,6	IV	-	-	M	151 (6%)	-	-	-	III	P	I	C	✓
47	12	M	40	MTC	NVP	I/LCS	Mix	+	↑	1,2,3	III, IV	+	+	DI	1051 (32%)	-	-	-	III	P	I	C	✓

48	8	F	10	MTC	-	H/LN	BF	+	↓	1,2,3	II, III	-	+	LZ	260 (8%)	-	-	-	IV	P	I	C	✓
49	5	M	11.2	MTC	-	I/LN	CM	-	↓	1,2,3	IV	+	-	LZ	505 (8%)	-	-	-	III	P	I	C	✓
50	4	M	11.5	MTC	-	H/LN	BF	+	↓	1,2,3	IV	-	-	UZ	575 (25%)	-	-	-	III	P	I	C	✓
51	10	F	19.5	MTC	-	H/LN	BF	-	↓	1,2,3	IV	-	-	LZ	425 (23%)	-	-	-	III	P	I	C	✓
52	5	F	13	MTC	-	I/LN	CM	-	↓	1,2,3	IV	-	-	UZ	538 (15%)	-	-	-	III	P	I	C	✓
53	11	M	24	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	LZ	237 (16%)	-	-	-	III	P	I	C	✓
54	8	M	15	MTC	-	I/LN	BF	-	↓	1,2,3	IV	+	-	LZ	205 (21%)	-	-	-	III	P	I	C	✓
55	10	F	20	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	-	692 (29%)	-	-	-	III	P	I	T	✓
56	5	M	15	MTC	-	I/LN	BF	+	↓	1,2,3	III	-	-	DI	212 (7%)	-	-	-	III	P	I	C	✓
57	7	M	16	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	LZ	609 (18%)	-	-	-	III	P	I	C	✓
58	10	F	14.8	MTC	-	I/LN	BF	+	↓	1,2,3	IV	+	-	UZ	918 (25%)	-	-	-	III	P	I	C	✓
59	10	F	14	MTC	-	I/LN	BF	+	↓	1,2,3	II, III, IV	-	-	DI	106 (10%)	-	-	-	III	P	I	C	✓
60	5	M	14	MTC	-	I/LN	Mix	-	↓	1,2,3	III, IV	-	-	UZ	893 (28%)	-	-	-	III	P	I	C	✓
61	3	M	10	MTC	-	I/LN	BF	-	↓	1,2,3	III, IV	-	-	PE	945 (12%)	-	-	-	III	P	I	C	✓
62	6	M	11	MTC	-	H/LN	BF	+	↓	4	I	-	-	-	576 (17%)	+	HEP, A, N	-	III	EP	I	C	✓
63	12	F	28	MTC	-	I/LCS	CM	+	↓	1,2,3	III, IV	+	-	DI	416 (15%)	-	-	-	III	P	I	IR	✓
64	7	M	19	MTC	-	I/LN	BF	+	↓	3,5	IV, V	-	-	DI	106 (4%)	-	-	-	III	EP	I	C	✓

65	5	M	10.5	MTC	-	I/LCS	CM	+	↓	1,2,3	III, IV	-	-	DI	624 (18%)	-	-	-	III	P	I	IR	✓
66	12	M	19	MTC	-	I/LN	BF	-	↓	1,2,3	II, IV	-	-	UZ	1299 (20%)	-	-	-	III	P	I	C	✓
67	10	M	23	MTC	-	I/LN	Mix	+	↓	1,2,3	II, IV	-	-	DI	135 (6%)	-	-	-	III	P	I	T	✓
68	11	F	18	MTC	-	H/LN	BF	+	↓	1,3,6	VI	-	-	-	117 (4%)	-	N	CSF+	IV	EP	I	D	✓
69	4	F	9	MTC	-	I/LN	BF	-	↓	1,2,3	III, IV	-	-	HA	1524 (32%)	-	-	-	III	P	I	C	✓
70	7	M	18	MTC	-	I/LCS	BF	-	↓	1,2,3	IV	-	-	MZ	378 (19%)	-	-	-	III	P	I	C	✓
71	5	M	13.6	MTC	-	I/LN	CM	-	↓	1,2,3	III, IV	-	-	LZ	1183 (19%)	-	-	-	III	P	I	C	✓
72	11	F	12.5	MTC	-	I/LN	BF	+	↓	1,2,3	III, IV	-	-	DI	512 (14%)	-	-	-	III	P	I	C	✓
73	5	M	15	MTC	-	I/LN	BF	+	↓	1,2,3	II, III	-	-	-	382 (16%)	-	-	-	III	P	I	C	✓
74	8	F	14	MTC	-	I/LN	BF	+	↓	1,2,3	IV	+	-	DI	266 (16%)	-	-	-	III	P	I	C	✓
75	3	M	10	MTC	-	H/LN	BF	+	↓	1,2,3	IV	-	-	DI	1163 (34%)	-	-	-	III	P	I	C	✓
76	3	F	8	MTC	-	I/LN	BF	-	↓	1,2, 3,6	IV	-	-	UZ	905 (19%)	-	-	-	III	P	I	C	✓
77	10	F	21	MTC	-	H/LN	BF	+	↓	1,2,3	IV	-	-	DI	698 (29%)	-	-	-	III	P	I	C	✓
78	8	F	13	MTC	-	I/LCS	BF	+	↓	1,2,3	I, III	-	-	DI	386 (20%)	-	-	-	III	P	I	C	✓
79	6	F	16	MTC	-	I/LN	BF	-	↓	4	IV	-	-	-	600 (13%)	+	-	-	III	EP	I	C	✓
80	5	M	13	MTC	-	I/LN	BF	-	↓	1,2,3	III, V	-	-	DI	449 (17%)	-	-	-	III	P	I	C	✓
81	11	M	20	UK	-	I/LN	BF	-	↓	2,3	IV	-	-	-	10 (2%)	-	HEP, N	-	IV	EP	I	D	✓

82	10	M	16	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	HA	81 (6%)	-	-	-	III	P	I	T	✓
83	5	F	15	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	DI	539 (12%)	-	-	-	III	P	I	C	✓
84	8	M	17	MTC	-	I/LN	CM	-	↓	3,4	I	-	-	-	554 (13%)	+	-	-	III	EP	I	C	✓
85	6	M	16	MTC	-	I/LN	BF	-	↓	1,2,3	IV	-	-	HA	495 (23%)	-	-	-	III	P	I	C	✓
86	10	M	26	MTC	-	I/LN	BF	-	↓	1,3,4	I	-	-	-	743 (16%)	+	-	-	III	P	I	C	✓
87	8	F	16	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	DI	574 (17%)	-	-	-	III	P	I	C	✓
88	9	F	18	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	DI	595 (29%)	-	-	-	III	P	I	C	✓
89	11	F	26	MTC	-	I/LN	BF	+	↓	1,2, 3,4	I	-	-	-	342 (21%)	+	-	-	III	EP	I	C	✓
90	5	M	14	MTC	-	I/LN	BF	+	↓	1,2	IV	-	-	B	615 (19%)	-	-	-	III	P	I	IR	✓
91	11	M	17	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	DI	777 (29%)	-	-	-	III	P	I	C	✓
92	3	F	9	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	LZ	576 (17%)	-	-	-	III	P	I	C	✓
93	7	M	38	MTC	-	I/LN	BF	-	↓	1	IV	-	-	TE	791 (32%)	-	-	-	III	P	I	C	✓
94	5	M	15	MTC	-	I/LCS	BF	-	↓	1,2	IV	-	-	DI	372 (18%)	-	-	-	III	P	I	C	✓
95	2	M	8	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	DI	890 (28%)	-	-	-	III	P	I	T	✓
96	9	M	18	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	HA	911 (25%)	-	-	-	III	P	I	C	✓
97	10	F	16	MTC	-	I/LN	BF	-	↓	1,2	IV	-	-	UZ	909 (20%)	-	-	-	III	P	I	C	✓
98	11	M	15	MTC	-	I/LN	BF	-	↓	1,2,3	III	+	-	M	31 (8%)	-	-	-	III	P	I	D	✓

99	11	F	12	MTC	-	I/LN	BF	+	↓	1,2,3	IV	-	-	MZ	84 (10%)	-	-	-	III	P	I	C	✓
100	9	F	15	MTC	-	I/LN	BF	+	↓	1,2,3	III, VI	-	-	-	180 (11%)	-	-	CSF+	IV	EP	I	C	✓

Abbreviations to Master Chart:

MTC - Mother to Child
BT - Blood Transmission
UK - Unknown
NVP - Nevirapine
POD - Place of Delivery
MOD - Mode of Delivery
I/LN - Institution / Labour Naturalis
I/LCS - Institution / Lower Caesarean Section
H/LN - Home / Labour Naturalis
BF - Breast Feed
CM - Cow's Milk
Mix - Mixed

Clinical Features

1 - Fever
2 - Cough
3 - Loss of appetite
4 - Lymphadenopathy
5 - Abdominal Pain

System Examination

I - Lymph Nodes
II - Skin
III- Oral Cavity
IV - Respiratory System
V - Abdomen
VI - CNS, Others

CXR

UZ - Upper Zone
MZ - Middle Zone
LZ - Lower Zone
M - Miliary
PE - Pleural Effusion
HA - Hilar Adenopathy
B - Bronchiectasis
DI - Diffuse Infiltrates
CS- Caries Spine

FNAC

USG Abdomen

HEP - Hepatomegaly
HSM - Hepatosplenomegaly
N - Nodes
Norm. - Normal
A - Ascites

ATT

P - Pulmonary
EP - Extra Pulmonary

Rx Outcome

C - Cured
D - Death
T - Transfer
DF - Default
IR - Irregular
Ctx - Cotrimoxazole Prophylaxis

6 - Seizures, Back Pain, etc.

+ : Granulomatous changes

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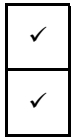

BIBILIOGRAPHY

1. Hershkovitz I, Donoghue HD, Minnikin DE, Besra GS, Lee OY-C, et al. (15 October 2008). "Detection and Molecular Characterization of 9000-Year-Old Mycobacterium tuberculosis from a Neolithic Settlement in the Eastern Mediterranean.". *PLoS ONE* **3** (10): e3426. doi:10.1371/journal.pone.0003426.
2. Zink A, Sola C, Reischl U, Grabner W, Rastogi N, Wolf H, Nerlich A (2003). "Characterization of Mycobacterium tuberculosis complex DNAs from Egyptian mummies by spoligotyping". *J Clin Microbiol* **41** (1): 359–67. doi:10.1128/JCM.41.1.359-367.2003. PMID 12517873
3. Hippocrates. Aphorisms. Accessed 7 October 2006.
4. Zur Pathogenie der Impetigines. Auszug aus einer brieflichen Mitteilung an den Herausgeber. [Müller's] *Archiv für Anatomie, Physiologie und wissenschaftliche Medicin*. 1839, page 82.
5. Nobel Foundation. The Nobel Prize in Physiology or Medicine 1905. Accessed 7 October 2006.
6. Tuberculosis *Encyclopedia Britannica*, 11th ed. Disseminated tuberculosis NIH Medical Encyclopedia. Accessed 9 October 2006.

7. Bhansali SK. "Abdominal tuberculosis. Experiences with 300 cases". *Am. J. Gastroenterol.* **67** (4): 324–37. PMID 879148
8. Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; & Mitchell, Richard N. (2007). *Robbins Basic Pathology* (8th ed.). Saunders Elsevier. pp. 516-522 ISBN 978-1-4160-2973-1
9. Onyebujoh, Phillip and Rook, Graham A. W. World Health Organization Disease Watch: Focus: Tuberculosis. December 2004. Accessed 7 October 2006.
10. Houben E, Nguyen L, Pieters J (2006). "Interaction of pathogenic mycobacteria with the host immune system". *Curr Opin Microbiol* **9** (1): 76–85. doi:10.1016/j.mib.2005.12.014. PMID 16406837
11. Herrmann J, Lagrange P (2005). "Dendritic cells and Mycobacterium tuberculosis: which is the Trojan horse?". *Pathol Biol (Paris)* **53** (1): 35–40. PMID 15620608.
12. Kaufmann S (2002). "Protection against tuberculosis: cytokines, T cells, and macrophages". *Ann Rheum Dis* **61 Suppl 2**: ii54–8. PMID 12379623
13. Houben E, Nguyen L, Pieters J (2006). "Interaction of pathogenic mycobacteria with the host immune system". *Curr Opin*

Microbiol **9** (1): 76–85. doi:10.1016/j.mib.2005.12.014. PMID 16406837

14. Grosset J (2003). "Mycobacterium tuberculosis in the extracellular compartment: an underestimated adversary". *Antimicrob Agents Chemother* **47** (3): 833–6. doi:10.1128/AAC.47.3.833-836.2003. PMID 12604509
15. Nelson Text book of Pediatrics 18th edition volume-I
16. Centers for Disease Control and Prevention (CDC), Division of Tuberculosis Elimination. Core Curriculum on Tuberculosis: What the Clinician Should Know. 4th edition (2000). Updated August 2003.
17. Nahid P, Pai M, Hopewell P (2006). "Advances in the diagnosis and treatment of tuberculosis". *Proc Am Thorac Soc* **3** (1): 103–10. doi:10.1513/pats.200511-119JH. PMID 16493157
18. Pai M, Zwerling A, Menzies D (June 2008). "Systematic Review: T-Cell-Based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update". *Ann. Intern. Med.* **149** (3): 1–9. PMID 18593687
19. Reddy JR, Kwang J, Lechtenberg KF, Khan NC, Prasad RB, Chengappa MM (January 2002). "An immunochromatographic serological assay for the diagnosis of Mycobacterium

tuberculosis". *Comp. Immunol. Microbiol. Infect. Dis.* **25** (1): 21–7. doi:10.1016/S0147-9571(01)00016-9. PMID 11831744.

20. HIV and TB: A guide for counsellors, New Delhi, Ministry of Health and Family welfare, NACO and Government of India.
21. Abrams EJ. Opportunistic Infections and other clinical manifestations of HIV disease in children. Pediatri Cli North Am 2000; 47:79-108
22. Mumbai Districts AIDS Control Society, Training manual for Doctors, New Delhi, NACO.
23. 2006 Report the committee on Infectious Diseases, 27th edition ELK Grove village, American Academy of Pediatrics 2006, PP 380-381; P 382
24. HIV infection codes and official guidelines for coding and reporting ICD-9-CM, MMWR Recomm. Rep 1994; 43(RR-12); 1-19
25. NACO 2003-available from: www.nacoonline.org guidelines/HIV-TB guidelines.
26. Corbett. Arch Intern Med 2003;163:1009-21. (s)
27. Raviglione MC, sinder DE, Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA 1995; 273:220-6

28. Paranjape RS, Tripathy SP, Menon PA etal. Increasing trend of HIV seroprevalence among pulmonary tuberculosis patients in Pune. Indian Journal Med Res 1997:106:207-11.
29. Merchant RS, Shroff RC. HIV seroprevalence in disseminated tuberculosis and chronic diarrhea. Indian Pediatr;35:883-7
30. Husson RN. Tuberculosis. In: Pizzo PA Wilfert CM (eds) Pediatric AIDS. 3rd edition. 1998;139-56
31. Misra SN, Sengupta D. AIDS in India:Southeast Asian J Trop Med Public Health 1998;29:37-6
32. Sharma SK, Mohan A. Co-infection of HIV and TB Indian perspective. Indian J Tuberc 2004;51:5-16
33. Bornschlegel K, Thomas P. Tuberculosis in children born to HIV infected human in New York City. XI International Conference on AIDS, Vancouvr, Canada. 1996.
34. Lederman MM, Georges DL, Kusner DJ. M.tuberculosis and its purified protein derivative activate expression of HIV. J Acquire immune Defic Syndr 1994; 7:727-33.
35. Zhang Y, Nakata K. M tuberculosis enhances HIV-1 replication by transcriptional activation at the long terminal repeat. J Clin Invest 1995;95:2324-31

36. Whalen C, Copathogenicity of tuberculosis and HIV disease. Clin Infec. Dis (In Press)
37. Harries AD. TB and HIV infection in developing countries. Lancet 1990; 335:387-90
38. Folks TM, Kinter A, Fauci AS. Cytokine-induced expression of HIV-1 in a chronically infected promonocyte cell line. Science; 238:800-2
39. Osoborn L, Kunkel S. TNF α and interleukin 1 stimulate the HIV enhancer by activation of nuclear factor kB. Proc Natl Acad Sci USA; 86:2336-40
40. Harries AD, Kangombe C et al. The scourge of HIV-related TB a cohort study in a district hospital in Malawi. Ann Trop Med Parasitol 1997;91:771-6
41. Perlman DC, Nelson ET et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of HIV-related immuno suppression. Clin Infect Dis 1997;25:242-6
42. Mukadi YD, Coulibaly IM et al. Impact of HIV infection on the development clinical presentation and outcome of tuberculosis among children in Abidjan, Cote d'Ivoire. AIDS 1997;11:1151-8
43. Topley JM, Bamber S. TB meningitis and co-infection with HIV. Ann Trop Pediatr 1998;18:261-6

44. Garay JE. Clinical presentation of pulmonary tuberculosis in under 10s and differences in AIDS-relatedcases: a cohort study of 115 patients. Trop Doctor 1997;27:139-42

45. Jeena PM, Mitha T, Bamber S, Wesly A, Coutsoudis A. Effects of the HIV on TB in children. Tuberc Lung Dis 1996;77:437-43

46. American Academy of Pediatrics, Committee on Pediatric AIDS. Evaluation and medical treatment of HIV-exposed infant. Pediatrics 1997;99:909-17

47. Johnson JL, Okwera et al. Impact of HIV-1 infection on the initial bacteriologic and radiographic manifestations of pulmonary TB in Uganda. Int J Tuberc Lung Dis 1998;2:397-404

48. Bekedam HJ, Kamenya A et al. Tuberculous lymphadenitis a diagnostic problem in areas of high prevalence of HIV and TB. Trans Roy Soc Trop Med HYg 1997;91:294-7

49. Centers for Disease Control and Prevention. Prevention and treatment of TB among patients infected HIV. MMWR 1998;47(RR-20):1-58

50. Moore M, McCray E, Castro KG. Trends in drug-resistant TB in United States, 1993-1996. JAMA 1997;278:833-7

51. CDC Initial therapy for tuberculosis in the era of multidrug resistance. Recommendations of the advisory council for the

elimination of TB MMWR North Mortal wkly Rep 1993;42 (RR-7):1-8

52. Bayer R, Wilkinson D. Directly observed therapy for TB: history of an idea Lancet 1995;345:1545-1548
53. Fox W. Self administration of medications. A review of published work and a study of problems. Bull int union Tuberc; 37:307-331
54. Chaisson RE, Holt EA et al. Six month supervised intermittent TB therapy in Haitian patients with and without HIV infection. Am J Respir Crit Care Med 1996;154:1034-8
55. Mitchison DA, Dickinson JM. Laboratory aspects of intermittent drug therapy. Postgrad Med J; 47:737-741
56. Narita M, Ashkin D. Paradoxical worsening of TB following anti-retroviral therapy in patients with AIDS. Am J Respir Crit Care Med 1998;158:157-61
57. O'Brien KL, Ruff AJ, Lous MA et al. Bacillus Calmette-Guerin complications in children born to HIV-1 infected women with a review of the literature. Pediatrics 1995;95:414-8
58. Bhat G, Diwan V, Masona J. HIV, BCG and TB in children. J Trop. Pediatr. 1993;39:219-23
59. Merchant RH, Oswal JS, et al, clinical profile of HIV infection. Indian Pediatr 2001;38:239-246.

60. Lodha R, Singhal T, Jain Y, et al. Pediatric HIV infection in a tertiary care centre in North India; early impression. Indian Pediatr 2000;37:982-986.

61. Dhurat R, Manglani M, Sharma M, et al. Clinical spectrum of HIV infection. Indian Pediatr 2000;37:831-836

62. Shahab T, Zoha MS, Afzal K et al. Prevalence of HIV in children with TB. Indian Pediatr 2004;41:595-599.

63. Cherian T, Verghese PV. TB and HIV infection. Indian J Pediatr 2000;67:S47-S52.

PROFORMA

TB MANIFESTATIONS IN PEDIATRIC HIV

- Name :
- Age / Sex:
- Address:
- Parent/Guardians Name & Address:
- Date of Sero positivity :
- Place of Sero positivity :
- Mode of Transmission :
    a) Mother to child :
    b) Blood transfusion:
    c) Other modes (sexual, injection etc.,)
    d) Unknown
- Mother ANC History : HAART / NVP / NIL
- Place of Delivery : Institution / Home
- Mode of Delivery :
    a) Labour Naturalis:
    b) Caesarean section: Elective / Emergency
    c) Vacuum
    d) Assisted forceps:

Infant feeding Duration :

a) Exclusive Breast feeding
b) Artificial feeding
c) Cow's milk
d) Mixed

- **Developmental Milestones : Normal / Abnormal**
- **FAMILY HISTORY**

Members	**Age / Sex**	**HIV Status**	**CD4**	**On ART Y/N**	**TB status Y/N**	**On ATT Y/N**
Father Mother Brothers Sisters Others						

Socio Economic H of Parent/Guardian:

Education Status:

Illiterate
Primary School
Higher Secondary
College

Employed : Yes/No

Occupation :

Per capita income :

Clinical Manifestations :

Fever :

Cough :

Breathlessness :

Loss of appetite :

Abdominal Pain :

Diarrhea :

Lymphadenopathy:

ALOC/ Seizures/mental deterioration:

Osteoarthritis :

Others

General Examination Height: Weight: MAC: BMI:

Built: (well) (moderate) (poor) (Febrile)	(pallor) (cyanosis) (Tachypnoeic) (pedal edema) (Jaundice) (others)
Lymph nodes: Y/N (Region) (Nos:) Cervical / Axillary / Others (Tender/non tender) (Matted/Discrete)	
Skin: (Normal) (PPE) (IBA) (Scabies) (Herpes Zoster) (Seb.derm) (Tinea) (xerosis) (others)	
Oral Cavity (Normal) (Oral candidiasis) (OHL) (Hyper pigmentation) (Aphthous ulcer) (Herpes simplex) (Angular stomatitis) (others)	
RS: (normal) (breath sounds) (added sounds) (others)	
CVS: (Normal) (Abnormal)	
Abdomen: (Normal) (Tenderness) (Organomegaly)	
Genitals: Normal / Abnormal	
CNS: (Normal) (Consciousness) (Neck stiffness) (plantar reflex) (DTR) (Memory) (Motor weakness) (Sensory signs) (visual disturbance)	

Immunisation H : BCG / OPV

Investigation :

Hb% :

TC :

DC :

ESR :

Sugar :

Urea :

Creatinine :

LFT :

Sputum for AFB 1. 2. 3.

Mantoux test :

CXR :

CD 4 Count / CD 4 % :

FNAC :

USG Abdomen :

CT Scan Brain :

CSF :

Others :

Δ : HIV $\bar{C}$ TB WHO Stage I / II / III / IV

TREATMENT HISTORY:

ATT

Pulmonary Sputum +ve/-ve Extra pulmonary	Category: I, II, III	• Date of Treatment Started Completed • Adherence Regular / Irregular • Treatment outcome • Cure • Treatment completed • Treatment Failure • Default • Died • Transfer out	Side Effects

Re infection

Relapse

Recurrence

Cotrimoxazole prophylaxis: Y / N Regular / Irregular

ART

Regimen : ZLN / ZLE / SLE / SLN

Date of treatment started:

Adherence: Good / Poor / occasionally missed

Reasons for missing:

Side Effects

IRIS: